Psoriasis in children and adolescents:
treatments and assessment measures

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Contents

List of abbreviations

A	area
ACH	acrodermatitis continua of hallopeau
AEs	adverse events
BMI	body mass index
BSA	body surface area
CADI	Cardiff Acne Disability Index
CAPTURE	continuous assessment of psoriasis treatment use registry
CDLQI	Children's Dermatology Life Quality Index
CI	confidence interval
D	desquamation
DFI	Dermatitis Family Impact
DLQI	Dermatology Life Quality Index
DMF	dimethylfumarate
DNA	deoxyribonucleic acid
E	erythema
EMA	European Medicines Agency
FAE	fumaric acid esters
FDA	Food and Drug Administration
GPP	generalized pustular psoriasis
H	head
HPA	hypothalamic-pituitary-adrenal
I	infiltration; induration
ICC	intraclass correlation coefficient
IL	interleukin
IQR	interquartile range
IRB	institutional review board
ISDL	Impact of Chronic Skin Disease on Daily Life
JIA	juvenile idiopathic arthritis
L	lower extremities
LOCF	last observation carried forward
LOE	level of evidence
MCID	minimal clinically important difference
MTX	methotrexate
NB-UVB	narrow band UVB
PaGA	Patient's Global Assessment
PASI	Psoriasis Area and Severity Index
PASI 75	75% improvement in PASI compared with baseline
PEASI	Psoriasis Exact Area and Severity Index
PGA	Physician's Global Assessment
PLASI	Psoriasis Log-based Area and Severity Index
PML	progressive multifocal leukoencephalopathy
PREPI	Patient Report of Extent of Psoriasis Involvement
PRO	patient-reported outcome
proSPI	professional version of the Simplified Psoriasis Index
proSPI-p	psychosocial impact component of the professional Simplified Psoriasis Index
proSPI-s	severity component of the professional Simplified Psoriasis Index
PUVA	psoralen and ultraviolet A phototherapy
Q	questions
QoL	quality of life
RCT	randomized controlled trial

RNA	ribonucleic acid
SAEs	serious adverse events
SAPASI	Self-Administered Psoriasis Area and Severity Index
saSPI	patient self-assessment version of the Simplified Psoriasis Index
saSPI-p	psychosocial impact component of the self-assessment Simplified Psoriasis Index
saSPI-s	severity component of the self-assessment Simplified Psoriasis Index
SD	standard deviation
SEM	standard error of the mean
SIFS	Stein Impact on Family Scale
SPI	Simplified Psoriasis Index
SPI-i	historical course and interventions component of the Simplified Psoriasis Index
SPI-p	psychosocial impact component of the Simplified Psoriasis Index
SPI-s	severity component of the Simplified Psoriasis Index
SPSS	statistical package for the social sciences
T	trunk
TNF	tumour necrosis factor
T-QoL	Teenager's Quality of Life Index
U	upper extremities
UV	ultraviolet
UVA	ultraviolet A
UVB	ultraviolet B
UVC	ultraviolet C
VAS	visual analogue scale
WC	waist circumference

Chapter 1

General introduction and outline of this thesis

1.1 Pediatric psoriasis

Psoriasis is a common, chronic, inflammatory skin disorder[1], with an estimated prevalence in western countries between 2-4%.[2-5] Disease onset can be at any age, but more than one third of the patients developed psoriasis during childhood.[6-9] Different prevalence rates of pediatric psoriasis are described, varying between 0% (Taiwan) to 2.1% (Italy).[2,5,7,10-15] In three studies from respectively Germany[10,14] and the United Kingdom[5], the prevalence of psoriasis in children in the first decade (0-9 years) was estimated between 0.18%-0.55%, whereas in the second decade (10-19 years) a prevalence rate of 0.83%-1.37% was reported. A Dutch study described a prevalence rate of 0.37% in children aged 0-10 years and 1.09% in patients aged 11-19 years.[7] In some studies on the epidemiology of pediatric psoriasis, an approximately linear increase in prevalence was suggested during the first 18 years.[10,14] Whereas in some studies girls were found to be much more often affected than boys[16-19], in others the reported gender distribution was approximately equal.[14,20-24] In a population-based study on the incidence of psoriasis in children in the United States, a more than two-fold increase in incidence was reported during a 30-year time period from 1970 to 2000.[24] The overall annual incidence rate (age- and sex-adjusted) in this study was 40.8 per 100.000 person-years.[2,24,25]

The most common clinical subtype of psoriasis in the pediatric population is plaque psoriasis (also referred to as psoriasis vulgaris)[19-24,26-32], followed by guttate psoriasis.[22-24,32] Other psoriasis subtypes e.g. pustular psoriasis, palmoplantar psoriasis, inverse psoriasis and erythrodermic psoriasis occur less frequently in children and adolescents.[21,23,26,29] Typical psoriatic lesions are characterized by well-defined, sharply demarcated erythemato-squamous papules and plaques of variable size which are scattered in a usually symmetrically distribution on the body.[33,34] In pediatric patients, lesions are usually smaller, thinner and less scaly than in adult patients.[21,27,29,30] Predilection sites of psoriasis are the extensor surface of elbow and knee, scalp, lumbosacral region and umbilicus.[33,34] In children and adolescents, the scalp is commonly affected[18-20,24,28,30] and involvement of the face and flexural areas is more common than in adult patients.[27,29] Involvement of the nails (nail plate and/or nail bed) appears in up to 40% of the pediatric patients[16,18-20,29,35], primarily nail pitting.[20,25,29] Other clinical manifestations of nail involvement include onycholysis, oil drop discoloration, subungual hyperkeratosis, splinter hemorrhages, red spots in the lunula, crumbling, leukonychia and beau's lines.[29,36-38]

1.2 Treatments in pediatric psoriasis

The treatment of psoriasis in the pediatric population poses some challenges.[27,29,30,39] First, there is only limited evidence on the efficacy and safety of treatments in children and adolescents with psoriasis.[40] In addition, most treatments are not licensed for use in

children.[29,30,39] In daily practice, therapeutic decision making is influenced by several factors, considering for example: age, disease severity, location and type of psoriasis, previous treatments, psychosocial impact, presence of comorbidities, practicality of the regimen, tolerability and safety, accessibility, costs and patient preferences.[25,27-30,41] To support caregivers in their treatment choices, evidence based data on the efficacy and safety of treatments in pediatric psoriasis are essential. As psoriasis is a chronic disease which currently cannot be cured[28,29], and treatments are given to children with a life-time ahead, particularly long-term safety data are indispensible.[41,42]

In this introduction the treatments which are commonly prescribed in pediatric psoriasis will be discussed. These comprise topical treatments (corticosteroids, vitamin D_3 analogues, calcineurin inhibitors, keratolytics, coal tar and dithranol), phototherapy, conventional systemic treatments (methotrexate, cyclosporine, retinoids, fumaric acid esters) and biologics. The evidence that was available at the start of this thesis will be described, and the lack of evidence or need for more information will be addressed. As our group published a systematic review on the efficacy and safety of treatments in pediatric psoriasis in 2010[40], much of the evidence described below, is revealed from that review.

Topical treatments

Corticosteroids

Corticosteroids have anti-inflammatory, anti-pruritic and anti-proliferative properties[28,43-45] and are the most commonly prescribed treatment in pediatric psoriasis.[32,46] There are numerous distinct topical steroids available, which differ from each other in their potency and the used vehicle.[32,47] In the Netherlands, four potency classes are distinguished.[47] In general, possible side effects of topical steroids can be distinguished in local cutaneous and/or systemic side effects.[44,47] Local cutaneous side effects include skin atrophy, periorificial dermatitis, striae distensae, telangiectasia, acne, folliculitis and purpura.[44,47] Possible systemic side effects encompass Cushing's syndrome, suppression of the hypothalamic-pituitary-adrenal (HPA) axis, osteoporosis, osteonecrosis, growth retardation, glaucoma and cataracts.[44,47] In younger children care should be taken to their higher body surface area to body weight ratio and consequently the increased risk on both cutaneous and systemic side effects.[42,44] To reduce the potential side effects of topical corticosteroids, it is recommended to use steroids intermittently and alternately with other nonsteroidal agents.[28,32,44] In addition, it is recommended to switch to lower-potency steroids when remission has been achieved.[44]

The evidence on the use of topical steroids in children and adolescents with psoriasis was found to be limited and of low level.[40] The majority of evidence is derived from two studies reporting the efficacy of halobetasol propionate 0.05% cream and ointment[48] and clobetasol propionate emulsion formulation foam 0.05%[49] respectively in a total of 20 patients for a treatment period of two weeks.[40] Reported side effects were relatively mild and include skin atrophy, erythema, depigmentation and burning.[40,48,49]

Vitamin D_3 analogues

The therapeutic effect of the vitamin D_3 analogues calcitriol (1,25-dihydroxyvitamin D_3) and calcipotriol (also called calcipotriene, a synthetic form of vitamin D_3)[45] is based on the inhibition of keratinocyte proliferation and deoxyribonucleic acid (DNA) synthesis and the promotion of keratinocyte differentiation.[28,31,44] From September 2011, monotherapy with calcipotriol is no longer available in the Netherlands[43], but calcitriol ointment is still available. Although calcitriol and calcipotriol are not registered for use in children and adolescents[43], vitamin D_3 analogues are considered to be important in the treatment of pediatric psoriasis.[40,43] Rotational therapy with mild-to-moderate topical corticosteroids is recommended[40,43] because of their synergistic and corticosteroid-sparing effect.[28,32] Most frequently occurring local side effects are skin irritation and pruritus.[40,43] Vitamin D_3 analogues are considered to be an effective and reasonably well-tolerated treatment option for pediatric psoriasis.[40,43]

Over recent years, a combination product including calcipotriol 50 µg g^{-1} and a potent corticosteroid (betamethasone dipropionate 0.5 mg g^{-1}) in *ointment* and *gel* vehicle has become available for the treatment of adult psoriasis.[43,50-53] In adults, both formulations have shown to be an effective and well-tolerated treatment option for psoriasis.[43,53] At the start of this PhD-project, data on the use of the two-compound *ointment* in pediatric psoriasis were lacking. Therefore, the effectiveness, safety and influence on the quality of life (QoL) of calcipotriol/betamethasone dipropionate *ointment* in pediatric psoriasis will be described in this thesis.

Calcineurin inhibitors

Tacrolimus ointment (0.03% and 0.1%) and pimecrolimus cream (1%) are calcineurin inhibitors. Their mechanism of action is based on the inhibition of the enzyme calcineurin, resulting in a decreased T-cell activation and proliferation and a decreased production of interleukin (IL)-2.[28,30,43] Topical tacrolimus 0.03% ointment and pimecrolimus 1% cream are approved for the treatment of atopic dermatitis in patients aged 2 years and above.[44,54] Tacrolimus 0.1% ointment is registered for atopic dermatitis patients aged ≥16 years.[54] After application burning, stinging or pruritus can occur.[28,32,43,44] In (pediatric) psoriasis calcineurin inhibitors are prescribed off-label.[28,43] Evidence on their use in pediatric psoriasis is scarce.[40] For short-term treatment of facial and intertriginous pediatric psoriasis, tacrolimus 0.1% ointment seemed to be effective and safe.[40]

Keratolytics

Keratolytics like topical salicylic acid, lactic acid and urea, are nonsteroidal agents which decrease hyperkeratosis and scaling by reducing intercellulair cohesion of keratinocyts.[28] They are generally used in conjunction with other topical agents.[28,32,44] Keratolytics containing salicylic acid should be prescribed with caution in young children because of the increased risk on salicylate intoxication.[28,30,32] To our knowledge, data on the effectiveness and safety of keratolytics in pediatric psoriasis are lacking.

Coal tar

Coal tar is a distillation product from coal which contains a huge number of different compounds including phenols, polycyclic aromatic hydrocarbons and heterocyclic compounds.[28,44] It is a well-known treatment option for inflammatory disorders including psoriasis because of its anti-pruritic and anti-proliferative effects.[28] The mechanism of action has recently been unraveled by van den Boogaard et al.[55] The use of coal tar can be limited because of its odor and staining of skin and clothes.[28,32,43,44] Potential side effects include folliculitis, irritant contact dermatitis and photosensitivity.[28,32,44] The use of topical and bath form coal tar in combination with phototherapy (Goeckermann regimen) in pediatric psoriasis is described in some studies.[28,56-58] However, to our knowledge, evidence on the use of coal tar as monotherapy in children and adolescents with psoriasis does not exist.

Dithranol

Dithranol (anthralin) therapy is a synthetic nonsteroidal agent which acts by its anti-proliferative and anti-inflammatory properties[28,32], although the exact pathogenic mechanism is not fully unraveled.[32,44] Two ways of application of dithranol are described: short-contact therapy (application during 10-30 minutes) versus classic 24-hours application.[43] Application is preferably in day care setting with frequent follow-up visits.[59,60] Potential side effects include local skin irritation and staining of skin and clothes.[25,28,30,44] Application should be avoided in erytrodermic, pustular, facial and intertriginous psoriasis.[28,30] In pediatric psoriasis, dithranol is considered to be an effective and safe treatment option[40,59,61], and is proposed when treatment with topical agents (calcipotriol, whether or not combined with mild-to-moderate topical corticosteroids) is ineffective or psoriasis is moderate-to-severe.[40]

Phototherapy and photochemotherapy

The spectrum of ultraviolet (UV) radiation can be distinguished in UVA (320-400 nm) which encompasses UVA-I (340-400 nm) and UVA-II (320-340 nm), UVB (290-320 nm) and UVC (200-290 nm).[62] For the treatment of psoriasis, phototherapy with UVB and UVA is generally used[43], whereby UVB only reaches the epidermis due to its shorter wavelength, while UVA gets access to both epidermis and dermis.[62] The therapeutic effect of phototherapy is based on a broad range of anti-inflammatory, anti-proliferative and immunosuppressant modalities.[43,62] Photochemotherapy is the combined use of phototherapy (generally UVA) and a (topical or systemic) photosensitizer like psoralens (PUVA).[43,62] In the Netherlands, treatment with PUVA in pediatric psoriasis is contra-indicated because of the risk of carcinogenesis.[43,63] The use of phototherapy as a treatment option in children and adolescents with psoriasis has been described in several publications, mostly reporting on narrow band UVB (NB-UVB, 311-313 nm).[28,62] In these studies NB-UVB showed beneficial effects on plaque and guttate pediatric psoriasis.[25,40,62]

Short-term side effects from phototherapy are usually mild and include in general xerosis, erythema, pruritus, blistering and photoactivation of herpes virus.[62,64] While premature photoaging and carcinogenesis are reported long-term side effects in adults treated with PUVA, the potential long-term carcinogenic risk of NB-UVB treatment is still subject of debate.[28,43,65-70] Furthermore, an increased number of sunburns during all life-periods has reported to be associated with an increased risk of melanoma.[71] To our knowledge, in children and adolescents with psoriasis long-term safety data in large studies on the use of NB-UVB treatment are not clearly reported so far.[40,43,62,72] Although there is a need for long-term safety data on phototherapy[73] in the pediatric psoriasis population, this will not be addressed in this thesis. In pediatric patients, especially anxiety, but also time commitment for patient and families and inconvenience could be problematic when using phototherapy.[40,62,74] According to the Dutch guideline, short-term NB-UVB could be considered in adolescents with psoriasis but has to be used carefully whereby special caution should be taken to those with fair skin.[40,43,63]

Systemic treatments

Methotrexate

Methotrexate (MTX) is a folic acid antagonist reversibly inhibiting the enzyme dihydrofolate reductase. It consequently inhibits thymidylate and purine synthesis resulting in decreased DNA and ribonucleic acid (RNA) synthesis and decreased repair and replication of T-and B-lymphocytes.[28,30,41,43] It has been used for the treatment of psoriasis since 1958.[43,75] Potential side effects include nausea, vomiting, fatigue, stomatitis, loss of appetite, bone marrow suppression, pulmonary toxicity, renal insufficiency, photosensitivity and hepatotoxicity including liver fibrosis.[28,30,41] In children and adolescents, MTX has not been approved for the treatment of psoriasis, but is used off-label.[41] Evidence on the efficacy and safety of MTX in children and adolescents is limited and only retrospectively collected.[40] The majority of evidence comes from three retrospective case series with a total of 32 children.[76-78] Based on this evidence, MTX was concluded to be an effective treatment option in moderate-to-severe pediatric psoriasis and it was proposed to be the first-line systemic treatment option in pediatric psoriasis.[40] Because of the lack of (prospective) evidence on the effectiveness and safety of MTX in pediatric psoriasis, we performed a prospective study on the effectiveness, safety and impact on QoL of MTX in pediatric psoriasis patients in daily clinical practice during this PhD-project which is described in this thesis.

Cyclosporine

Cyclosporine is an immunosuppressant drug, that binds to the intracellular protein cyclophilin and therefore selectively inhibits calcineurin resulting in a reversibly inhibitory effect on T-lymphocytes and suppression of IL-2 and interferon-γ.[28,30,41,75] Clinical improvement can occur within 2-4 weeks after start.[28] Possible side effects include

nephrotoxicity, hypertension, nausea, vomiting, diarrhea, myalgias, arthralgias, headache, gingival hyperplasia, paresthesia, hypertrichosis and immunosuppression thereby increasing the risk of lymphoproliferative disorders and other malignancies and infections.[28,30,41,43,64,75] In pediatric psoriasis, cyclosporine is not approved for use.[30,41] The use of cyclosporine in pediatric psoriasis has only sparsely been described in case series and case reports.[40] Although there was a need for more evidence on cyclosporine in pediatric psoriasis, we did not address this question in this thesis. However, in the discussion the newest evidence will be presented.

Retinoids

Retinoids are vitamin A derivates which affect the cellular metabolism, epidermal differentiation, and apoptosis by binding to the nuclear receptors in keratinocytes.[28,30,64] Most of the evidence in pediatric psoriasis was found on etretinate[40], which is no longer available.[43,75] Evidence on acitretin in pediatric psoriasis is scarce.[40] Potential side effects include cheilitis, xerosis, epistaxis, skin fragility, ocular toxicities and hair thinning.[25,30,64] Skeletal changes are described in children using long-term retinoid treatment.[30,40,64,79] In infants and male adolescents with pustular and erytrodermic psoriasis, short-term treatment with retinoids can be considered.[40] Cause for concern includes the high teratogenic risk of retinoids.[30,64,79] Therefore, in females and women of child-bearing potential effective contraceptive measures are obligatory during and up to at least two years after discontinuation of therapy.[43,63,75]

Fumaric acid esters

The immunomodulatory effects of fumaric acid esters (FAE) are diverse and primarily based on the active ingredient dimethylfumarate (DMF).[43,75,80] Although FAE are described in the European guideline[75], they are not registered in the Netherlands.[43,63] In the Netherlands different FAE formulations are available, including monotherapy with DMF as well as mixtures of DMF and three salts of ethyl hydrogen fumarate.[43,75] Despite the fact that FAE are not approved, they are widely used in adults with psoriasis. The majority of evidence on the use of FAE in pediatric psoriasis comes from a Dutch retrospective case series of 14 children in which FAE seemed to be effective and safe.[81] Gastrointestinal complaints, flushing, temporary shifts in leukocytes, increased liver enzymes, proteinuria and elevated serum creatinine levels were reported as side effects in this retrospective case series.[81] In this thesis, a prospective case series on FAE in recalcitrant pediatric plaque-type psoriasis is described.

Biologics

Biologics, or biologicals, are recombinant proteins which selectively interfere with specific components of the inflammatory cascade in the pathogenesis of psoriasis.[28,30,64,82] At the beginning of this PhD-project, etanercept (Enbrel®), a fully human soluble tumour necrosis

factor (TNF)-receptor fusion protein that competitively inhibits the binding of endogenous TNF-α to its receptor[30,41,75], was the only biological which was approved by the European Medicines Agency (EMA) for the treatment of chronic severe pediatric plaque-type psoriasis (age ≥ 6 years) in case of ineffectiveness or intolerance to other systemic treatments or phototherapy.[83,84] Very recently, the first data on the use of two other biologics in pediatric psoriasis have become available: adalimumab and ustekinumab. These data will be described in the discussion of this thesis.

Psychosocial support

Another additional treatment modality to medical treatments in pediatric psoriasis includes patient education and psychosocial support.[28,30,31] To our knowledge, the evidence on training programmes in children and adolescents with psoriasis is limited to one inpatient education programme performed in Germany.[85] In this particular study an inpatient treatment group (n = 34) was compared to a control group of 21 children and adolescents with former inpatient rehabilitation, but without education, resulting in improved skills of disease management, long-term self-estimated skin condition and psychosocial impairment.[85] In 2011, our group developed an outpatient multidisciplinary training programme for children and adolescents with psoriasis and their parents.[86] In a case-study, its development and design was illustrated.[86] In this thesis, the efficacy of this multidisciplinary outpatient training programme is evaluated in a pilot study.

1.3 Assessment measures on disease severity and psychosocial impact

Psoriasis severity

It is important to assess psoriasis severity as precisely as possible for optimal therapeutic decision-making. In addition, it allows caregivers to monitor changes induced by treatment. Therefore, valid and reliable measures to assess psoriasis severity are indispensable.[87-89] To the best of our knowledge, validated psoriasis severity measures in children and adolescents are lacking. In adult psoriasis patients, a wide variety of psoriasis severity measures exist[87-91], which are summarized in two systematic reviews from 2010.[87,89] Nowadays, the most widely used psoriasis severity measure for scientific evaluation is the Psoriasis Area and Severity Index (PASI).[75,87,89,92]

PASI has originally been developed in 1978.[75,93] To calculate the PASI score, four body regions (Head, H; Upper extremities, U; Trunk, T; Lower extremities, L) are separately assessed for severity of the lesions and percentage of the involved area in a body region. These four body regions (Head, Upper extremities, Trunk and Lower extremities) account for 10%, 20%, 30% and 40% of the total body surface area respectively. In each body region, disease severity is measured by assessing erythema (E), infiltration (I) and

desquamation (D) on a five-point scale (range 0-4; 0, no involvement; 1, slight; 2, moderate; 3, marked; 4, very marked). In addition, the percentage of involved body surface area per body region (A) is assessed using a seven-point scale (0, no involvement; 1,<10%; 2, 10<30%; 3, 30<50%; 4, 50<70%; 5, 70<90%; 6, 90–100%).[88,94,95] PASI is calculated by the following formula:
$PASI = 0.1A_h (E_h + I_h + D_h) + 0.2A_u (E_u + I_u + D_u) + 0.3A_t (E_t + I_t + D_t) + 0.4A_l (E_l + I_l + D_l)$. PASI ranges from 0 to 72 with higher scores indicating more severe psoriasis.[88]

PASI is reported to be the most extensively studied psoriasis severity measure and is recommended to assess psoriasis severity in a research setting.[87] PASI is also often used as a reference standard for the validation of new severity measures.[89,92] Furthermore, PASI has been incorporated in the established European treatment goals for moderate-to-severe psoriasis.[96] In these treatment goals and also in the European guideline for the treatment of psoriasis, an improvement in PASI of 75% or more (PASI 75) is defined as a clinically meaningful endpoint.[75,91,96] PASI, however, has been criticized by having a number of shortcomings.[87,89,91,92] A frequently reported limitation encompasses PASI being not able to assess small affected areas in a body region.[89,91,97-99] Because of this need to assess small affected areas in a body region (<10% of a body region) as precisely as possible, we aimed to develop a refined PASI score for psoriasis patients with small affected areas (Low PASI), which is described in this thesis.

Two other frequently used psoriasis severity measures are the percentage of the affected body surface area (BSA) and the Physician's Global Assessment (PGA).[75,100] The BSA can be assessed by counting the involved body area by the number of patients' handprints.[89] One handprint of the patient (palm plus 5 digits) is approximately equivalent to 1% of the total BSA in children and <1% of the total BSA in adults.[101,102] Another way to estimate BSA is using the 'rule of nines', dividing the total body area in several smaller areas each counting for 9% of the total BSA, with 1% leaving for the genital area.[89,103] The other commonly used severity measure is the PGA.[75,89,100,104] The PGA assesses the overall psoriasis severity using an ordinal rating scale. Several PGA scales are available, varying in the number of ratings. The assessment can be done static (at one moment in time) or dynamic (compared to baseline severity).[89]

Psychosocial impact

To assess the impact of psoriasis on the physical, social and psychological functioning of those affected, patient-reported outcome (PRO) measures can be used.[105] Their approach can be *generic, dermatology-specific* or *psoriasis- specific*.[75,105,106] A major construct in PRO measures is health-related quality of life.[107] As quality of life (QoL) can be affected by many factors other than health, the more restricted term 'health-related QoL' is used when evaluating the effects of health status including disease and treatment on physical, psychological and social functioning and well-being of the patient.[108] The impact of psoriasis on the QoL in children and adolescents can be profound.[109-115]

To the best of our knowledge, *psoriasis-specific* QoL questionnaires designed for use in children and adolescents do not exist[116], apart from the Scalpdex which has been validated for children (aged 6-18 years) with scalp psoriasis.[117] To assess QoL in pediatric psoriasis, a *dermatology-specific* questionnaire can be used. There are some validated *dermatology-specific* questionnaires available for use in children and adolescents (e.g. the Children's Dermatology Life Quality Index (CDLQI)[118], the Skindex-Teen[119] and the Teenagers' Quality of Life (T-QoL©) Index.[120] As a comprehensive review of *all available measures to assess psychosocial impact (*including *generic)* in children and adolescents is out of the scope of this thesis, only the assessment measures which are used in this thesis, will be described below.

Children's Dermatology Life Quality Index

In children with psoriasis the CDLQI is a widely used *dermatology-specific* QoL instrument.[118] The CDLQI has been validated in children with different skin diseases aged 4 to 16 years.[118] It consists of ten questions concerning itch/pain, embarrassment, friendships, clothing, going out/playing/doing hobbies, swimming/sports, school/holiday, teasing/bullying/asking questions/avoiding, sleep and treatment.[118] These questions (Q) encompass six headings on symptoms and feelings (Q1-2), leisure (Q4-6), school or holidays (Q7), personal relationships (Q3,8), sleep (Q9) and treatment (Q10).[121] The CDLQI evaluates patients' perceptions from the last week. Each question is scored on a four-point Likert scale (0, not at all; 1, only a little; 2, quite a lot, 3, very much) resulting in a total score ranging from 0 to 30. More impairment of QoL is indicated by higher scores.[118,121,122] In 2003 Holme et al. validated a cartoon version of the CDLQI, which was faster and easier for children to use.[123]

Dermatology Life Quality Index

In patients aged 16 years and above, the Dermatology Life Quality Index (DLQI)[124] is a commonly used *dermatology-specific* questionnaire to assess QoL. The DLQI was developed and validated in 1994 to assess QoL in patients (≥16 years) with various skin conditions.[124] Just like the CDLQI, the DLQI encompasses ten questions using a four-point Likert scale (0, not at all/not relevant; 3, very much; range 0-30) and more impact on QoL is indicated by higher scores.[124-126] The ten questions of the DLQI concern itch/pain, embarrassment, shopping/looking after home or garden, clothing, social or leisure activities, sports, work/study, problems with partners/close friends/relatives, sexual difficulties and treatment.[124] These questions encompass the following headings: symptoms and feelings (Q1-2), daily activities (Q3-4), leisure (Q5-6), work or school (Q7), personal relationships (Q8-9), and treatment (Q10).[125,126] The questions concern patients' perception during last week.[124]

Impact of Chronic Skin Disease on Daily Life

The Impact of Chronic Skin Disease on Daily Life (ISDL) is a *dermatology-specific* and *generic* health instrument.[127] In the *dermatology-specific* part of this multidimensional health

status inventory, dimensions of physical functioning (skin status; physical symptoms of itch, pain and fatigue; scratching responses) and disease-related stressors including stigmatization are assessed. In the *generic part* of this inventory dimensions of psychological functioning, disease-related impact, illness cognitions and social support are concerned. The ISDL has been validated in adult patients with psoriasis and atopic dermatitis.[127]

Stein Impact on Family Scale

The Stein Impact on Family Scale (SIFS) is a *generic* questionnaire which measures the perceived reactions of a family member of the effects of the child's ongoing health condition on family life. For our study we used the revised version in which 15 items are used to calculate the Total Impact on Family Score.[128,129] Each item is scored using a four-point scale (1, strongly agree; 4, strongly disagree).[128] The total score therefore ranges from 15 to 60 with lower scores indicating more impact on family life.[129]

Dermatitis Family Impact questionnaire

The Dermatitis Family Impact (DFI) questionnaire was developed by Lawson et al. to assess the impact of childhood atopic dermatitis on family life.[130,131] The DFI has to be filled out by the parent or caregiver and consists of a ten-item questionnaire concerning the impact on housework, food, sleep, leisure, time shopping, expenditure, tiredness and/or exhaustion, emotional distress, relationships and treatment.[130] The questions regard the impact from the last week. Each question is scored on a four-point scale ranging from 0 to 3 (0, not at all; 1, a little; 2, a lot; 3, very much). This results in a total score ranging from 0 to 30.[130,131]

Composite measure – the Simplified Psoriasis Index

The measures as mentioned before in this introduction, assess either disease severity or psychosocial impact. In 2013 a new summary measure was published: the Simplified Psoriasis Index (SPI).[92] The SPI is a composite assessment measure which is derived from the Salford Psoriasis Index.[92,132] The SPI consists of three separate components: first a disease severity component (SPI-s), second a psychosocial impact (SPI-p) component and third a historical course and response to therapeutic interventions component (SPI-i).[92] There are two versions available which are complementary and can be completed by a health professional (proSPI) or by patient self-assessment (saSPI).[92]

The first domain of the SPI (SPI-s) (Figure 1, part 1) encompasses a composite severity score in which disease *extent* is multiplied by an *overall disease severity* score. To assess the *extent* of psoriasis, ten unequal areas of the body are measured using a three-point scale (0, absent or minimal; 0.5, noticeable; 1, extensive) resulting in a total score ranging from 0-10. The ten areas which are assessed are: 1) scalp and hairline; 2) face, neck and ears; 3) arms and armpits; 4) hands, fingers and fingernails; 5) chest and abdomen (stomach); 6) back and shoulders; 7) genital area and/or around the anus (back passage); 8) buttocks and thighs; 9) knees, lower legs, and ankles; 10) feet, toes, and toenails. The scores for

Figure 1 Dutch version of the self-assessment Simplified Psoriasis Index (saSPI).

(adjusted from: Chularojanamontri L, Griffiths CE, Chalmers RJ. The Simplified Psoriasis Index (SPI): a practical tool for assessing psoriasis. J Invest Dermatol 2013; 133: 1956-62).[92]

Simplified Psoriasis Index
Zelfrapportage vragenlijst

Datum:

Bedankt voor het invullen van deze vragenlijst. Deze vragenlijst helpt ons om een indruk te krijgen hoe ernstig de psoriasis is. Je mag de vragenlijst ook samen met (een van) je ouders invullen. De vragen bestaan uit 3 gedeelten en vertellen ons een beetje hoe (ernstig) je psoriasis nu is, hoe vervelend jij je huid vond en hoe de psoriasis vroeger was. Als je vragen hebt over deze vragenlijst, vraag dit dan aan de verpleegkundige of de onderzoeker.

Hieronder mag je aangeven waar je nu psoriasis hebt.

DEEL 1A Hieronder staan 10 gebieden van het lichaam. Omcirkel voor elk gebied 1 keuze die het beste je psoriasis **vandaag** beschrijft.

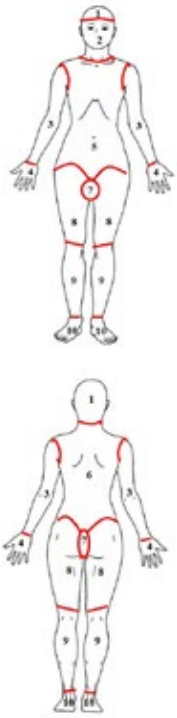
0	±	+

0	Geen plekken of zo weinig dat het nauwelijks opvalt (0)
±	Duidelijk aanwezig, maar nog steeds veel normale huid aanwezig (0.5)
+	Wijdverspreid over een groot gedeelte van het gebied (1.0)

1	**Behaarde hoofdhuid & haargrens**	0	±	+
2	**Gezicht, nek & oren**	0	±	+
3	**Armen & oksels**	0	±	+
4	**Handen, vingers & vingernagels***	0	±	+
5	**Borst & buik**	0	±	+
6	**Rug & schouders**	0	±	+
7	**Schaamstreek en/of rond de anus (bilspleet)**	0	±	+
8	**Billen & bovenbenen**	0	±	+
9	**Knieen, onderbenen & enkels**	0	±	+
10	**Voeten, tenen & teennagels***	0	±	+

*PSORIASIS VAN DE NAGELS: Als minstens 2 nagels ernstige psoriasis hebben (bijvoorbeeld: putjes *én* witte vlekjes *of* rode vlekjes *of* afbrokkelen van de nagelplaat of loslating *of* verdikking van het nagelbed), mag je **±** omcirkelen, zelfs als er geen psoriasis zit op de huid van je handen of voeten. Bij 6 vinger of teennagels mag je **+** omcirkelen.

SOM



DEEL 1B **Omcirkel** welk van onderstaande keuzes de psoriasis plekken die je **vandaag** hebt het beste beschrijft. Geef een score voor het **gemiddelde** van je psoriasisplekken, scoor dus **niet** alleen de plekken die het meest ernstig zijn. **Om je te helpen bij het scoren van je psoriasis mag je de voorbeeldfoto's gebruiken.**

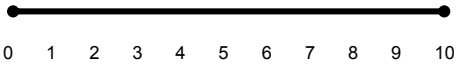
0	Geen roodheid of alleen lichte roodheid of verkleuring
1	Milde roodheid of schilfering met een klein beetje verdikking
2	Duidelijke roodheid, schilfering of verdikking
3	Matig ernstig met duidelijk meer roodheid, schilfering of verdikking
4	Zeer rood en geïrriteerd, veel schilfering of verdikking
5	Hevig geïrriteerde huid met of zonder puistjes (plekjes met pus)

PRODUCT 1A X 1B

Zie achterkant

Figure 1 Continued.

DEEL 2 Zet een streepje op de lijn hieronder dat het beste aangeeft hoe vervelend jij je huid **vandaag** vindt en hoeveel last je ervan hebt (bijvoorbeeld: last van een pijnlijke, jeukende of stekende huid; jezelf schamen of niet prettig voelen over je huid; bij het omgaan met vrienden/ vriendinnen; verwisselen van kleren/ schoenen; bij uitgaan, spelen of hobby's; bij zwemmen of andere sporten; op school of op vakantie; ben je gepest of uitgescholden of hebben mensen aan je gevraagd wat je had; bij het slapen; problemen met de behandeling).



Score: 0 = ik heb helemaal geen last van mijn psoriasis; ik kan alles doen wat ik wil
5 = door mijn huid heb ik (best) veel moeite om de dingen te doen die ik zou willen doen
10 = ik heb heel veel last van mijn psoriasis (ik kan me niet voorstellen dat het nog erger kan zijn)

DEEL 3 Hieronder staan een aantal beweringen. Kruis het hokje achter de zin aan als je denkt dat de bewering voor jou klopt. Laat het hokje leeg als je niet zeker bent of als je de behandeling niet kent.	Punt
Over je psoriasis	
Ik heb al meer dan 10 jaar psoriasis	
De psoriasis is voor mijn 10e jaar ontstaan	
Ik heb een zeer geïrriteerde psoriasis gehad van mijn **hele huid** (mijn hele huid was rood en/of mijn huid was geïrriteerd met puistjes)	
Ik ben opgenomen in het ziekenhuis voor mijn psoriasis.	
Over je psoriasis behandeling	
Ik heb minstens 1x lichttherapie gehad (UV-B of PUVA)	
Ik ben behandeld met methotrexaat (nu of in het verleden)	
Ik ben behandeld met acitretine (Neotigason, etretinaat) (nu of in het verleden)	
Ik ben behandeld met ciclosporine (Neoral) (nu of in het verleden)	
Ik ben behandeld met een "biological" gegeven door een injectie of infuus (nu of in het verleden) Biologicals zijn Remicade/infliximab; Enbrel/etanercept; Raptiva/efalizumab; Humira/adalimumab; Stelara/ustekinumab	
Ik ben behandeld met een ander tablet/ injectie behandeling voor mijn psoriasis (nu of in het verleden). Als dat zo is, kan je de naam van de behandeling nog herinneren? Naam van de behandeling: …….	
Wil je nakijken of je alle vragen hebt beantwoord. Dank voor je medewerking.	SUM

Dit wordt ingevuld door de arts of verpleegkundige

Deel 1	Deel 2	Deel 3
S	P	I
SEVERITY (0-50)	**P**SYCHOSOCIAAL (0-10)	**I**NTERVENTIE (0-10)

hands en feet include the possibility to score nail disease (0.5 if severe psoriasis of at least two and 1 for six or more finger or toenails affected). The *overall psoriasis severity* is scored using a six-point average plaque severity score resulting from 0 to 5. The SPI-s is derived by the multiplication of the psoriasis *extent* score (0-10) and the *overall severity* score (0-5) resulting in a maximum score of 50.[92]

The second domain of the SPI (SPI-p) (Figure 1, part 2) consists of a 10-cm visual analogue scale line which is converted to the nearest integer, resulting in a score ranging from 0 to 10.[92] The third domain of the SPI (Figure 1, part 3) includes a historical course and intervention score (SPI-i). The SPI-i incorporates four questions about historical course and six questions about therapeutic interventions, resulting in a score ranging from 0 to 10.[92] The total score of the SPI is presented as three separate scores for SPI-s (0-50), SPI-p (0-10) and SPI-i (0-10).[92] The validation and reliability of the SPI have already been shown in adult psoriasis patients.[92] In pediatric psoriasis, data on the validation of the SPI do not exist.

1.4 Daily clinical practice registry

The Child-CAPTURE registry (Continuous Assessment of Psoriasis Treatment Use Registry) is a prospective, longitudinal, long-term, single center pediatric psoriasis registry which was set up in 2008 at the department of Dermatology at the Radboud university medical center. In this registry daily clinical practice data on the effectiveness, safety and impact on QoL of all children and adolescents with psoriasis visiting the outpatient clinic are collected. At the moment, 340 children are included and inclusion of patients is still ongoing. The prospective data described in this thesis, are mainly extracted from the Child-CAPTURE registry.

1.5 Aims and outline of this thesis

This thesis on children and adolescents with psoriasis focuses on treatments and assessment measures.

The first part of this thesis **(Chapter 2)** concentrates on **therapeutic interventions** in children and adolescents with psoriasis. As mentioned before, at the beginning of this PhD-project, evidence on the effectiveness and safety of treatments in pediatric psoriasis was limited. In addition, most evidence was of low level.[40] In 2010, our group proposed an evidence-based treatment algorithm for pediatric psoriasis based on a systematic review of the literature on efficacy and safety of treatments in this patient group.[40] Over recent years however, more evidence has become available, and in addition, this thesis aimed to add evidence to the existing literature. First of all, we aimed to investigate the effectiveness,

safety and influence on the QoL of calcipotriol/ betamethasone dipropionate ointment in a prospective, daily clinical practice cohort of pediatric psoriasis patients **(Chapter 2.1)**. A two-compound formulation containing calcipotriol 50 µg g^{-1} and a potent corticosteroid (betamethasone dipropionate 0.5 mg g^{-1}) in *ointment* and *gel* vehicle has become available for adults.[43,50-53] However, evidence on the use of this two-compound formulation in *ointment* vehicle in pediatric psoriasis does not exist. As topical treatments are first-line and used in the majority of the pediatric psoriasis population[28,40,42,46], we considered it very important to investigate the effectiveness, safety and influence on QoL of this two-compound *ointment* in pediatric psoriasis.

Second, we aimed to provide a systematic overview on the efficacy and safety of systemic treatments in children and adolescents with psoriasis **(Chapter 2.2)** as recently, several overview articles on systemic treatments in pediatric psoriasis have been published[27,28,31,39,41,42,64,133,134] and in this vulnerable patient group, evidence-based data on efficacy and safety of systemics are indispensable to support clinical therapeutic decision making.

Based upon the conclusions from the previous publication from 2010[40] and the newly retrieved evidence in this systematic update, two conventional systemic treatments with limited and only retrospectively collected evidence, were further investigated in this thesis. The conventional systemic treatments of interest in this thesis were MTX and FAE. The effectiveness of MTX in pediatric plaque-type psoriasis in daily clinical practice was investigated prospectively in **Chapter 2.3**. Data were extracted from the Child-CAPTURE registry. Furthermore, the safety, influence on the QoL, 48- and 96-week drug survival, and the influence of body mass index (BMI) and waist circumference (WC) on the effectiveness of MTX were described. **Chapter 2.4** includes a prospective, daily clinical practice case series on the effectiveness, influence on QoL and safety of FAE in recalcitrant pediatric psoriasis.

However, treatment of pediatric psoriasis encompasses more than the prescription of medicinal products. In children and adolescents psychological well-being can be negatively affected by their psoriasis.[109-115] Therefore, an important additional treatment intervention includes patient education and psychosocial support.[25,28,30,31] As the evidence on educational training programmes in pediatric psoriasis was rare[85], in 2011 a multidisciplinary training programme for children and adolescents with psoriasis and their parents was developed in our center.[86] Its development and design are already described in a case-study suggesting that it could be a promising addition to regular treatment.[86] However, its efficacy has not been evaluated. In **Chapter 2.5** the effects of this multidisciplinary training programme on patient and parent satisfaction, QoL, itch and scratch responses, illness cognitions and impact on family life are presented.

The second part of this thesis **(Chapter 3)** focuses on **assessment measures on psoriasis severity and psychosocial impact**. To evaluate treatment response as precisely as possible, valid and reliable psoriasis severity measures are very important. In the adult literature, PASI[93] is the most commonly used and the most extensively studied psoriasis severity measure.[75,87,89] However, PASI has been criticized by having some shortcomings.[87,89,91,92] A major and commonly reported limitation addresses PASI being not able to assess small affected areas in a body region.[89,91,97-99] To monitor differences in psoriasis severity before- and after treatment in patients with minimal involvement (lower than 10% of a body region), accurate assessment of these small affected areas in a body region is essential. Therefore, we developed a refined PASI score for psoriasis patients with small affected areas, called Low PASI. In **Chapter 3.1** the Low PASI score is presented and compared with the classic PASI. Furthermore, the interobserver agreement of the classic PASI and the Low PASI was evaluated and the two scores were compared within both investigators.

In addition to the monitoring of psoriasis severity as described before, it is also important to assess the impact of psoriasis on the physical, social and psychological functioning of those affected.[75,135-137] In pediatric psoriasis, the CDLQI[118] is a commonly used *dermatology-specific* measure to assess QoL, whereas in patients aged 16 years and older, the DLQI[124] is widely used. In psoriasis patients aged 16-17 years, it is not known whether DLQI and CDLQI reflect QoL in the same way. Therefore, we aimed to examine and compare the DLQI and CDLQI scores in adolescents aged 16-17 years with psoriasis **(Chapter 3.2).**

Abovementioned assessment measures encompass either only disease severity or only QoL. Recently, a new psoriasis assessment measure has been developed which includes both aspects: the SPI.[92] The SPI can be assessed by the health professional (proSPI) or by patient self-assessment (saSPI) and has recently been validated in adults with psoriasis.[92] In children and adolescents, data on the SPI do not exist. To our knowledge, evidence on composite measures to assess both disease severity and QoL in pediatric psoriasis in general are missing. Therefore, we aimed to validate the severity (SPI-s) and psychosocial impact (SPI-p) domains of the professional and patient self-assessment SPI in children and adolescents with psoriasis (**Chapter 3.3).**

In summary, the following aims were defined:

Treatments

1. To investigate prospectively the effectiveness, safety and influence on quality of life of calcipotriol/betamethasone dipropionate ointment in pediatric psoriasis in daily clinical practice.
2. To present a systematic overview on the efficacy and safety of systemic treatments in pediatric psoriasis.
3. To investigate prospectively the effectiveness, safety and the influence on quality of life of methotrexate in pediatric psoriasis in daily clinical practice.
4. To study prospectively the effectiveness, influence on quality of life and safety of fumaric acid esters in pediatric psoriasis in daily clinical practice.
5. To explore the efficacy of an outpatient multidisciplinary training programme for children and adolescents with psoriasis and their parents.

Assessment measures on disease severity and psychosocial impact

6. To develop a refined PASI score for patients with small affected areas (Low PASI).
7. To compare DLQI and CDLQI scores in psoriasis patients aged 16-17 years.
8. To investigate the criterion validity, construct validity, and response distribution of the severity (SPI-s) and psychosocial impact (SPI-p) domains of the professional and self-assessment versions of SPI in children and adolescents with psoriasis.

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Chapter 2

Treatments

2.1

Calcipotriol/betamethasone dipropionate ointment in mild-to-moderate pediatric psoriasis: long-term daily clinical practice data in a prospective cohort

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Abstract

Background: Psoriasis in children has a significant negative impact on the quality of life (QoL) and effective treatment can improve this. The two-compound ointment calcipotriol 50 µg g^{-1} and betamethasone dipropionate 0.5 mg g^{-1} is an effective treatment option for moderate-to-severe psoriasis in adults.

Objectives: To study prospectively the effectiveness and safety of calcipotriol/betamethasone dipropionate ointment in pediatric patients with mild-to-moderate plaque psoriasis in daily clinical practice and to investigate the influence on QoL.

Methods: Data were obtained from a prospective, longitudinal pediatric psoriasis registry, called Child-CAPTURE. Severity was assessed using the Psoriasis Area and Severity Index (PASI) and body surface area (BSA). The Children's Dermatology Life Quality Index (CDLQI) was used to assess QoL and visual analogue scores (VAS) for pain and itch were collected. For safety data the number of (serious) adverse events was recorded.

Results: Seventy-three patients (mean age 10.8 years, range 3-18) were treated for a median time of 35.0 weeks (range 1.0-176.0). At week 12, mean PASI decreased 15.4% (from 5.2 to 4.4), BSA barely changed, and median CDLQI decreased significantly from 5.5 to 4.0. VAS scores for pain and itch declined. At week 24, mean PASI decreased to 4.3 (17.3%). No related serious adverse events were observed.

Conclusions: In this daily clinical practice study in pediatric psoriasis, calcipotriol/betamethasone dipropionate ointment initially improved mild-to-moderate psoriasis and then maintained its effect. In addition, it improved QoL, with few adverse events.

Introduction

Psoriasis is a chronic, inflammatory skin disease that affects 2-3% of the general population. In approximately 30% of patients first symptoms appear during childhood.[1, 2] Psoriasis may have a significant negative impact on the quality of life in children and effective treatment can improve this quality of life.[3] Therefore, knowledge about therapeutic options in pediatric psoriasis is important, but so far, evidence is limited.

Currently, there is no cure for psoriasis and therapy is aimed at suppressing psoriatic lesions and relieving associated symptoms.[4] de Jager *et al.*[5] concluded in their systematic review that the treatment of choice in mild or moderate pediatric psoriasis should be topical treatment with calcipotriol, if necessary, combined with mild-to-moderate topical corticosteroids.

Recently, a two-compound ointment containing calcipotriol 50 μg g^{-1} and betamethasone dipropionate 0.5 mg g^{-1} has been developed in order to avoid separate applications and to improve patient compliance.[6] Several studies in adults have already demonstrated that this combination of calcipotriol and betamethasone dipropionate is more effective than either of the individual components and is well tolerated in short-term follow-up.[6-10] However, to date, evidence on the effectiveness and safety of calcipotriol/betamethasone dipropionate ointment in pediatric psoriasis is lacking. In addition, there are no data on the daily clinical management of unselected pediatric patients with psoriasis, nor on long-term effectiveness and safety of this therapy in children.

In this study we aimed to evaluate the effectiveness and safety of calcipotriol/betamethasone dipropionate ointment therapy in a prospective longitudinal cohort of pediatric patients with mild-to-moderate plaque psoriasis in daily clinical practice. In addition, we investigated the influence of this two-compound treatment option on the quality of life of those affected.

Patients and methods

Study design

This study was a descriptive, single-group, prospective observational daily clinical practice study enrolling children with psoriasis treated with calcipotriol/betamethasone dipropionate ointment. This study was carried out in the Netherlands in accordance with the applicable rules concerning the review of research ethics committees and informed consent.

Study population

All children with psoriasis receiving calcipotriol/betamethasone dipropionate ointment at our medical center between September 2008 and June 2013 were enrolled in this study.

Data were obtained from a prospective longitudinal pediatric psoriasis registry, called Child-CAPTURE (Continuous Assessment of Psoriasis Treatment Use Registry). The Child-CAPTURE was set up in September 2008 to monitor the effectiveness, safety and quality of life in all pediatric patients with psoriasis (age ≤ 18 years) who visited our outpatient clinic at the Radboud University Medical Center.[3]

Exclusion criteria were: current use of calcipotriol/betamethasone dipropionate ointment prior to enrolment; use of systemic antipsoriatic treatment (and therefore patients with severe psoriasis and psoriatic arthritis), phototherapy, or dithranol therapy within 6 weeks before the start or during calcipotriol/betamethasone dipropionate ointment treatment; or absence of any follow-up visit.

Study procedures

At baseline patient characteristics were recorded, including age, sex, age at onset, family history, medical history, presence of psoriatic arthritis, present and previous antipsoriatic treatments on all areas of the body and concomitant medication. At each visit disease severity scores [Psoriasis Area and Severity Index (PASI), physician's global assessment (PGA), body surface area (BSA), visual analogues scores (VAS) on itch and pain], concomitant therapies, a quality of life score [Children's Dermatology Life Quality Index (CDLQI)] and the occurrence of (serious) adverse events were recorded.

In a daily clinical practice setting, patients were provided with the best treatment and care according to the physician's opinion, but only two different treatment regimens were used dependent on the severity of psoriasis. In the more intensive treatment regimen patients were prescribed the ointment for once-daily use for 4 weeks, followed by prescription once daily four times per week. In the less intensive regimen patients were assigned to once-daily application four times per week directly from the start of treatment and thereafter. Appointments and the need for a new visit were made in dialogue with patient and parents; consequently follow-up was highly variable due to the daily clinical practice design.

Use of topical treatments other than calcipotriol/betamethasone dipropionate ointment on the scalp, face, folds and genital areas was allowed.

Outcome measures

The extent and the severity of the disease were assessed by a physician using the PASI (range 0–72).[11] A six-point scale PGA was used by the physician as an overall assessment of the severity of psoriasis graded from 0 to 5 ('clear', 'minimal', 'mild', 'moderate', 'severe' or 'very severe'). Also, the percentage of the total body surface (BSA) affected by psoriasis was recorded. VAS (range 0-100) scores were recorded as a measure for severity of itch and pain resulting from psoriatic lesions.

To quantify the impact of psoriasis on the children's quality of life, a validated Dutch version of the CDLQI was used (10 items; range 0–30).[12, 13] Higher scores indicate more

impairment in quality of life. All adverse events noted by the investigator or addressed by the patient (or parents) were recorded.

The primary objective of this study was the change in PASI score compared with baseline. Secondary objectives included changes in BSA, PGA and VAS, improvement in quality of life and safety data on (serious) adverse events.

Statistical analysis

PASI scores were interpolated to obtain outcome measures at weeks 2, 4, 8, 12, 24 and 48 after the start of treatment as time to follow-up in our cohort was variable due to the daily clinical setting. Analysis was made according to an as-treated principle (analysing continuing patients only according to follow-up). Subgroup analyses on PASI scores were performed on two groups with different treatment regimens.

The secondary outcomes (PGA, BSA, VAS and CDLQI) were analysed at visits at 12 weeks (window ± 4 weeks) using the Wilcoxon signed-rank test. If patients had multiple treatment episodes with the two-compound ointment, only the first episode was analysed, in order to avoid selection bias. All serious adverse events were recorded and the relationship with the use of study medication was described.

P-values < 0.05 (two-sided) were considered statistically significant. The statistical analyses were performed using SPSS software 20.0 (IBM Corp., Armonk, NY, U.S.A.) and Microsoft Office Excel 2007 SP3 MSO (Microsoft Corporation, Redmond, WA, USA).

Results

Patients

From September 2008, 147 children with psoriasis were prospectively treated with calcipotriol/ bethamethasone dipropionate ointment. A total of 73 patients were included in this study (Figure 1). Fifty-six per cent of the patients were female; the mean age at the start of calcipotriol/betamethasone dipropionate ointment was 10.8 years (Table 1).

No significant differences were found between the patients in the two different treatment regimens with respect to age, sex, age at first diagnosis or duration in weeks of the two-compound ointment use.

The median duration of calcipotriol/betamethasone dipropionate assignment until data lock was 35 weeks (range 1-176). At the time of analysis, calcipotriol/betamethasone dipropionate ointment was prescribed to 34 patients (47%). In 17 patients (23%), the calcipotriol/betamethasone dipropionate ointment did not yield a sufficient response and was ceased, whereas in 12 patients (16%) in their opinion the ointment became redundant because of a successful response. Six patients (8%) admitted stopping the treatment because they were not motivated to apply the ointment. Two patients (3%) only used calcipotriol/betamethasone dipropionate ointment to tide them over a period

Table 1 Patient characteristics for the total study population (n = 73).

Characteristic		
Sex, male, *n* (%)	32	(43.8)
Age at diagnosis (years), mean (range)	7.8	(1-16)
Age at starting use of ointment (years), mean (range)	10.8	(3-18)
Duration of calcipotriol/betamethasone dipropionate ointment use (weeks), median (range)	35.0	(1.0-176.0)
Calcipotriol/betamethasone dipropionate ointment discontinued, *n* (%)		
No	34	(46.6)
Yes	39	(53.4)
Treatment regimen, *n* (%)		
Starting once daily seven times per week during 4 weeks, followed by prescription once daily four times weekly	50	(68.5)
Starting once daily four times weekly and thereafter	23	(31.5)
With/without concomitant vitamin D ointment treatment 3 days a week, *n* (%)		
Without	26	(35.6)
With	47	(64.4)
Previous calcipotriol/betamethasone dipropionate ointment use, *n* (%)		
No	40	(54.8)
Yes	33	(45.2)
Concomitant therapies on specific areas of the body, *n* (%)		
Scalp	64	(87.7)
Face	41	(56.2)
Genital area	16	(21.9)
Folds	3	(4.1)
Ears	20	(27.4)

until the start of dithranol (anthralin) treatment. Two patients (3%) were lost to follow-up (Figure 1).

The median duration of calcipotriol/betamethasone dipropionate ointment use in the 39 patients who stopped using the ointment was 22 weeks (range 1-141). Of the 17 patients who yielded an insufficient response, 11 switched to dithranol (anthralin) treatment, three to phototherapy and one to methotrexate. One patient tried another topical corticosteroid (mometasone furoate) with additional calcipotriol ointment and one patient switched to a two-compound ointment containing betamethasone dipropionate and salicylic acid.

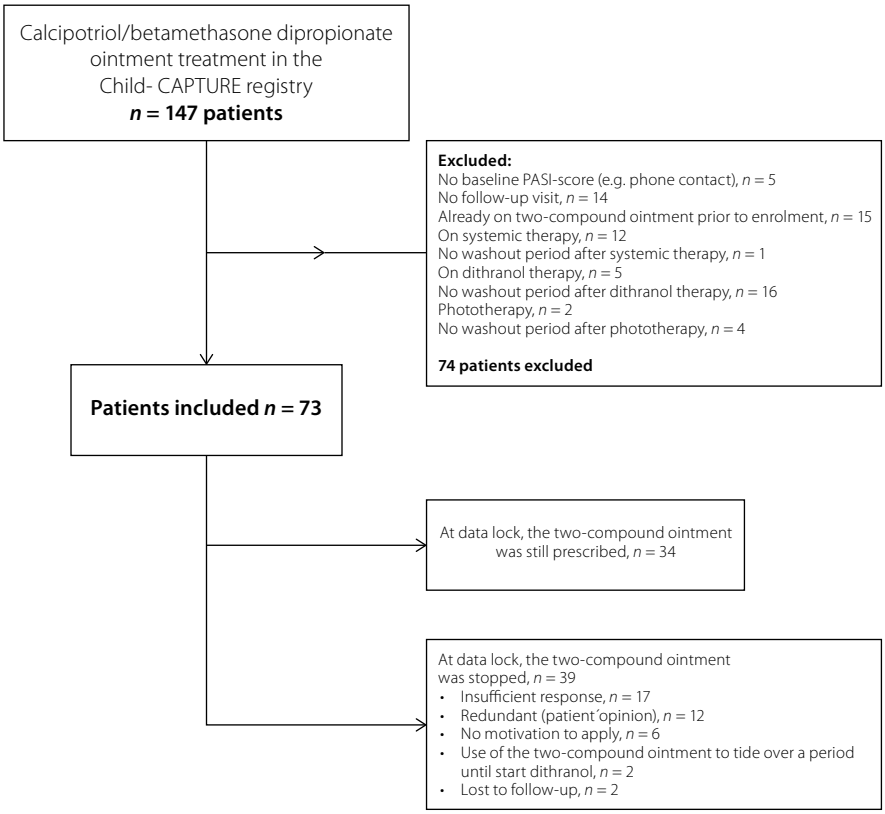

Figure 1 Flow chart on inclusion and exclusion of patients using calcipotriol/betamethasone dipropionate ointment.

CAPTURE, Continuous Assessment of Psoriasis Treatment Use Registry; PASI, Psoriasis Area and Severity Index.

Primary outcomes

The mean PASI score before treatment with calcipotriol/betamethasone dipropionate ointment was 5.2 (range 0-11.5). The mean PASI scores for the total population (*n* = 73) at weeks 2, 4, 8, 12, 24 and 48 are displayed in Figure 2. At 12 weeks, patients who were still treated (*n* = 61) achieved a decrease in mean PASI score of 15.4% (from 5.2 to 4.4). After 24 weeks the mean PASI score was slightly decreased to 4.3 (range 0.3-8.9), which was a decrease from baseline of 17.3%. After 48 weeks the mean PASI score was 3.4 (range 0-7.3), which was a 34.6% improvement compared with baseline. However, at 48 weeks the PASI score was based on the data of only 25 patients.

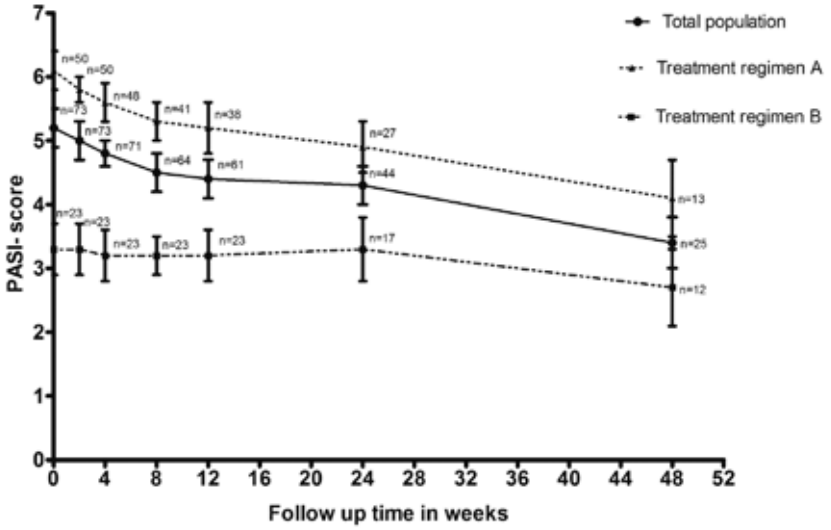

Figure 2 Psoriasis Area and Severity Index (PASI) score in time (as-treated analysis).

Treatment regimen A, starting once daily seven times per week for 4 weeks, followed by prescription once daily four times weekly; treatment regimen B, starting once daily four times weekly.

In Figure 2 different lines are plotted for the total population and split for two different treatment regimens. Fifty patients (68%) were prescribed the more intensive treatment regimen starting with application of the ointment once daily for 4 weeks. Twenty-three patients (32%) were assigned to once-daily application four times per week directly from the start of treatment. As depicted in Figure 2, patients who were prescribed the more intensive treatment regimen had significant higher baseline PASI scores (mean PASI 6.1 vs. 3.3). In this intensive treatment regimen group the mean PASI score decreased from 6.1 (range 2.6-11.5) at baseline to 4.9 (1.9-8.9) after 24 weeks, which was a decrease of 19.7%. In the group with the less intensive treatment regimen the mean PASI score remained stable from 3.3 (0-8.7) at baseline to 3.3 (0.3-8.1) at 24 weeks. Of the earlier described 17 patients who did not yield a sufficient response, two patients were prescribed the less intensive treatment regimen.

Secondary outcomes

At baseline the median CDLQI score was 5.5 [interquartile range (IQR) 3.0-9.0] compared with a median CDLQI score of 4.0 (IQR 2.3-7.8) after 12 weeks (Table 2). This included an absolute improvement of 1.5 points, which was statistically significant (Table 2). The distribution of the PGA scores was not statistically different at 12 weeks treatment compared with baseline.

Table 2 Secondary outcome measures for total population after 12 weeks of treatment.

Outcome measure	*n*	Median baseline score (IQR)		Median score after 12 weeks (IQR)		Absolute change in score	*P*-value[a]
CDLQI	36	5.5	(3.0-9.0)	4.0	(2.3-7.8)	-1.5	0.02*
PGA	41	2.0	(2.0-3.0)	2.0	(1.0-2.5)	0	0.68
BSA	41	4.5	(3.0-7.6)	4.9	(2.0-7.0)	+0.4	0.72
VAS pain	33	2.0	(0-15.5)	0.0	(0-4.5)	-2.0	0.04*
VAS itch	33	33.0	(15.0-60.0)	15.0	(3.5-43.0)	-18.0	0.05

BSA, body surface area; CDLQI, Children's Dermatology Life Quality Index; IQR, interquartile range; PGA, physician's global assessment; VAS, visual analogue score; [a] Wilcoxon signed-rank test. * $P < 0.05$.

All children included in the study had < 30% of body involvement. The affected BSA barely differed before and after treatment. The median VAS on pain decreased from 2.0 (IQR 0-15.5) to 0 (IQR 0-4.5) after 12 weeks, which was statistically significant. The median VAS on itch decreased from 33.0 (IQR 15.0-60.0) to 15.0 (IQR 3.5-43.0). Thirty-two patients reported both a CDLQI and a VAS itch at baseline and at week 12. At week 12, 50% of patients achieved CDLQI 0-1 and/or VAS itch ≤ 10 compared with 25% at baseline.

Safety

In total, five patients (7%) reported, or were observed to have, possible treatment-related adverse events. Four patients had striation of the skin: a 12-year-old girl had striations on the medial side of the upper legs after gaining weight in puberty; a 13-year-old girl had vertical striations on the upper legs and horizontal striations on the mammae and flanks; a 17-year-old boy had striations on the elbows and abdomen after gaining 10 kg in weight; and a 15-year-old boy had horizontal striations on the upper legs, arm pits and buttocks after a fast increase in body length. One girl experienced pain when applying the ointment at the location of a scar after surgery. No serious adverse events were reported.

Discussion

In this study we present a large, prospective, daily clinical practice cohort of pediatric patients with psoriasis with long-term follow-up. Several studies on calcipotriol/betamethasone dipropionate ointment have been performed on adults, but nearly all of these focus on induction therapy only.[6-10] Because of the chronic nature of the disease,[14] data on long-term effectiveness and safety are essential. Especially for children with mild-to-moderate psoriasis, more evidence on topical treatments is needed, as most of these children are primarily treated with topical treatment.

We found a decrease in mean PASI score of 15.4% and 17.3% at weeks 12 and 24, respectively, compared with baseline. This is less than observed in previous trials in which adults were treated with calcipotriol/betamethasone dipropionate ointment. [6-10] In these randomized controlled trials (RCTs), adult patients were treated for only 4-12 weeks and baseline PASI scores were mostly around 10. In these studies, 68.2-74.4% improvement from the baseline PASI score was found.[6-10] As our study comprised children with mostly mild psoriasis,[15] the mean baseline PASI score was 5.2. With a PASI score near 3, the percentage of each segment affected with psoriasis is usually < 10%. Consequently, reductions in the area affected with psoriasis are usually not associated with improvements in PASI.[7] Therefore, when scores are low, PASI may be a less precise tool for measuring the severity of psoriasis and effectiveness of a treatment.[7,16] In addition, most of the studies in adults were clinical trials with a washout period not only for systemic, but also for topical treatments. As this is a daily clinical practice study, a washout period for topical corticosteroids was not performed.

As stated before, the adult RCTs were performed over a relatively short period of time, with an active treatment period of only 4-12 weeks.[6-10] In these studies, a rapid improvement of psoriasis was seen, even as soon as after 1 week of treatment.[7-10] We also found that calcipotriol/ betamethasone dipropionate ointment seems to yield most of its effect in pediatric psoriasis in the first 12 weeks after the start of treatment. This may indicate that the largest effect of calcipotriol/ betamethasone dipropionate ointment is achieved in the first weeks. When used over a longer period as maintenance therapy it seems to stabilize psoriasis. In only one study, adult patients were followed for 52-weeks.[17] However, the main interest of that study was safety data; effectiveness was a secondary objective and only measured using PGA. The time between visits is a critical factor affecting adherence and outcomes.[18] This study had fewer return visits than typical clinical trials do. Without those visits to drive adherence, patients probably do not use the medication nearly as well as they do in clinical trials.

Subgroup analyses on the PASI score were performed based on a more or less intensive treatment regimen during the first 4 weeks of treatment. Patients who were prescribed the more intensive treatment regimen had higher baseline PASI scores and consequently yielded more effect from the two-compound ointment than the less intensively treated group (19.7% vs. 0%, respectively, after 24 weeks). Patients with more severe disease are likely to yield more effect from any treatment than less affected patients, in part because of regression to the mean, or to the greater sensitivity of the PASI in patients with more severe disease.

We recorded the CDLQI as a patient-reported outcome for quality of life at baseline and at 12 weeks follow-up. Despite a limited decrease in PASI score, the CDLQI decreased significantly after 12 weeks of treatment.

In our study possible treatment-related adverse events were reported in five children (7%), of which four had striation of the skin. Striae however, are common in adolescents

and occur frequently in association with adolescent growth spurts[19] and obesity.[20] Because all of these children grew during the study period and had used other topical treatments in the past, it is questionable whether these striations were related to the use of calcipotriol/betamethasone dipropionate ointment or not. No serious adverse events were reported.

The daily clinical practice design of this study resulted in variable time to follow-up and consequently interpolated PASI scores. It has to be taken into account that the mean PASI score at 48 weeks of treatment was based on only 25 patients. Therefore, this score may be less reliable as the remaining population becomes different from the original one. This may lead to attrition bias and consequently the remaining results may not be generalizable to the original population. Another limitation of real clinical practice analysis in general is the absence of a control group or parallel treatment group to compare, and the fact that we do not have data on adherence.

In conclusion, this study comprised a large, prospective cohort of children with psoriasis in daily clinical practice with a long-term follow-up period. Treatment with calcipotriol/betamethasone dipropionate ointment yielded a mild reduction in PASI score of 17.3% with only a few observed side effects and no severe adverse events. Our data indicate that this two-compound ointment first improves and then stabilizes mild-to-moderate plaque psoriasis during a long-term follow-up period in pediatric psoriasis.

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2.2

Systemic treatments in pediatric psoriasis: a systematic evidence-based update

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Abstract

In 2008, a systematic review revealed that evidence-based data on efficacy and safety of treatments in pediatric psoriasis are scarce and with low level of evidence. In recent years, publications on this topic have increased exponentially. To present a systematic, evidence-based update on the efficacy and safety of systemic treatments in pediatric psoriasis and to provide treatment recommendations, an update of the previous review was performed. PubMed, EMBASE and the Cochrane Controlled Clinical Trial Register were searched between January 2007 and March 2014 for all available literature on efficacy and safety of all systemic treatments in pediatric psoriasis. The levels of evidence were determined on the Oxford Centre for Evidence-based Medicine Levels of Evidence. The newly retrieved evidence was combined with the evidence available in the former review. Fifty-two studies were included: 36 from the former review, plus 16 new articles. New evidence on induction therapy was mainly available on fumaric acid esters (FAE), which are shown to be effective in a subgroup of patients. Long-term (96 weeks) safety and efficacy data on etanercept were found. Prospective studies are scarce. Most conclusions are formulated on studies with low level of evidence. Of the conventional systemic treatments, methotrexate still has the most evidence albeit in a low number of patients and with a low level of evidence. FAE seem to be effective in a subgroup of patients, with gastrointestinal complaints, flushes and temporary shifts in leukocyte counts and liver enzymes being the main side effects. Etanercept has still accumulated most evidence of the available systematic treatments, with a large efficacy and reassuring safety profile in a 96-week follow-up.

Introduction

Psoriasis is a chronic inflammatory skin disease that affects 2%-4% of the Caucasian population.[1,2] In about 30% of these patients, the disease manifests during childhood.[3] Systemic treatments are indicated in children with moderate-to-severe psoriasis. To date, evidence on efficacy and safety of systemic treatments in pediatric psoriasis is limited and evidence-based guidelines are scarce.[4] In 2010, our group published a systematic review of all available literature on efficacy and safety of treatments in pediatric psoriasis in the period January 1980 till September 2008.[4] This review provided evidence-based recommendations in which methotrexate (MTX) was considered the systemic therapy of choice, whereas retinoids should be considered in pustular and erythrodermic psoriasis. In exceptional cases, cyclosporine could be deliberated and etanercept was thought to be a third-line drug.[4]

Nowadays, the interest in pediatric psoriasis is emerging and the number of publications on systemic treatments in pediatric psoriasis has increased exponentially.[5-14] Therefore, the present review aims to present a systematic update on efficacy and safety of all systemic treatments in pediatric psoriasis in order to provide evidence-based recommendations with grading of evidence for this specific patient-group.

Methods

The literature on treatments between 1980 and September 2008 has already been searched and reviewed in a former publication.[4] Therefore, we conducted an extensive search on all available literature concerning systemic treatments of pediatric psoriasis, published between January 2007 and March 2014, on PubMed, EMBASE and the Cochrane Controlled Clinical Trial Register. To avoid an inaccurate lack of evidence, publication date was extended to January 2007, to include an overlapping time-frame. The search strategy and eligibility criteria were identical to our former study,[4] to which we refer for further information. In the present study, only systemic therapy was searched for.

After the initial search was performed, two reviewers (M.v.G and K.M.) independently screened titles and abstracts for inclusion and exclusion. Of the 1008 studies found between January 2007 and March 2014, in total 47 articles were assessed full-text. Of these 47 articles, 31 were excluded as they did not fit the inclusion criteria or they were already assessed in the previous search.[4] Finally, 16 articles were included in the new search. In addition, the previously found 36 full-text articles from the period between 1980 and September 2008 were assessed again. Thus, in total, 52 articles (16 new articles plus the 36 articles from the previous review) were included in this review.

A pre-designed data extraction form was used by the same two reviewers to independently extract and record the data from each full-text article. If no consensus was

reached, a third investigator (M.S.) was consulted. Levels of Evidence (LOEs) (Table 1) and grading recommendations (A-D) (Table 2) were determined according to the Oxford Centre for Evidence-based Medicine Levels of Evidence.[15]

Table 1 Level of evidence (LOE).

1a	Systematic review of RCTs
1b	Individual RCT
2a	Systematic review of cohort studies
2b	Individual cohort study (including low quality RCT)
3a	Systematic review of case-control studies
3b	Individual case-control study
4	Case series
5	Case reports, expert opinion

Adapted from 'Oxford Centre for Evidence-based Medicine Levels of Evidence' version May 2001.[15]
RCT, Randomized controlled trial.

Table 2 Grades of recommendation.

A	Studies with consistent LOE 1a and/or 1b (see Table 1)
B	Studies with consistent LOE 2a, 2b, 3a, or 3b; or extrapolations from studies with LOE 1a or 1b
C	Studies with LOE 4 or extrapolations from studies with LOE 2a, 2b, 3a, or 3b.
D	Studies with LOE 5 or troublingly inconsistent or inconclusive studies of any level

Adapted from 'Oxford Centre for Evidence-based Medicine Levels of Evidence' version May 2001.[15]
LOE, Level of evidence.

Results

The details on all 52 included studies are summarized in Table 3. In the section below, a short summary of the previous review[4] and the new evidence is described. The recommendations are based on all 52 included studies.

Antibiotics

The previous review included five studies[16-20] in which 14 pediatric patients with psoriasis were treated with antibiotics. It was concluded that the efficacy of the use of antibiotics in pediatric guttate psoriasis remains controversial.[4]

In the present review no new articles were included.

Conclusion

Grade C.

Number of patients treated with antibiotics: 14.

The efficacy of the use of antibiotics in pediatric guttate psoriasis still remains controversial.[4]

Retinoids

Previous review described six studies[21-26] with a total of 21 children treated with etretinate. Etretinate was considered to be an effective treatment for pustular and erythrodermic psoriasis but side effects were frequently seen,[4] being cheilitis, pruritus and hairloss.[21-23,25] The use of acitretin had not been sufficiently investigated, therefore no conclusions could be drawn.[4]

In the present review, eight new studies on the use of retinoids were identified.[27-34] Five studies were excluded because of systemic antipsoriatic combination therapy[27,30-33] and one study because of an unclear treatment regimen.[34] One case report[28] (LOE5) described clearance after 6 weeks of treatment with acitretin 1 mg/kg/day in a 6-weeks-old girl with generalized pustular psoriasis (GPP); safety data were not reported. The occurrence of a pseudotumour cerebri in a 12-year-old boy with GPP using oral acitretin 25-35 mg/day was presented in another case report; efficacy data were not included in this review due to an unclear outcome measure (LOE5).[29] As the two new cases described the use of acitretin in GPP, the evidence on the efficacy and safety of retinoids is still mainly shown in pustular and erythrodermic pediatric psoriasis.

Conclusion

Grade C.

Number of patients treated with retinoids: 24.

In pustular and erythrodermic pediatric psoriasis, retinoids are an effective treatment with frequently reported side effects.[4] Most evidence is still available on etretinate. As the use of acitretin is only described in three cases, no conclusions could be drawn.

Table 3 Summary of included studies.

Treatment	Author	LOE	Diagnosis (no. of patients)	Study type	No. of patients (age)
Antibiotics					
Thiamphenicol	Juanqin *et al.*[16]	4	GPP (2)	RCS	2 (2-12 y)
Amoxicillin/ clavulanic acid	Pacifico *et al.*[17]	5	GP (1)	CR	1 (7 y)
Erythromycin	Patrizi *et al.*[18]	4	GP (4)	CS	4 (5-10 y)
Rifampin	Rosenberg *et al.*[19]	4	GP (3); PP (1)	RCT	4 (5-10 y)
Erythromycin or penicillin V with addition of rifampin	Vincent *et al.*[20]	4	GP (3)	OL	3 (12-15 y)
Retinoids					
Acitretin	Chao *et al.*[28]	5	GPP (1)	CR	1 (6 wk)
Acitretin	Sarkar *et al.*[29]	5	GPP (1)	CR	1 (12 y)
Acitretin	Salleras *et al.*[24]	5	EP (1)	CR	1 (4 y)
Etretinate	Rosinska *et al.*[25]	4	EP (5); GPP (5)	RCS	10 (3-15 y)
Etretinate	van de Kerkhof[26]	5	GPP (1)	CR	1 (1 y)
Etretinate	Pavicic *et al.*[23]	4	GPP (5)	CS	5 (3- 11 y)

	Dose regimen	Duration of treatment	Outcome	Safety
	20 mg/kg/d	-	< 50% Clearance: 100%	Gastrointestinal disturbance
	50 mg/kg/d	20 d	Cleared: 100%	n.m.
	50mg/kg/d	2 wk	Psoriasis completely resolved: 100%	n.m.
		5 d	Excellent response: 25%; Good response: 75%	n.m.
		14 d	No clinical change: 100%	n.m.
	1 – 0.4 mg/kg/d	34 wk (6 wk to normalize)	Clearance: 100%	n.m.
	25-35 mg/d	6 wk	Excluded	Pseudotumour cerebri
	0.5 -0.75 mg/kg/d	3 mo	Complete remission: 100%	No secondary effects
	1 – 0.2 mg/kg/d	3 wk -12+ mo	EP: 2x complete clearing; 3x improvement; GPP: 5x complete clearing	Pruritus (8); cheilitis (7); skin fragility (7); hair loss (2); musculoskeletal pain (2). Focal osteoporosis of left tibia (1). Elevated serum transaminases level and positive hepatitis B s-antigen, developed glomerulonefritis preceded by varicella (1)
	10 mg/d	3 mo	Complete clearance: 100%	No adverse effects related to etretinate
	1 mg/kg /d	-	Complete and significant regression of erythroderma: 100%	Cheilitis (2); pruritus (1), transient diffuse effluvium (1); paronychia (1)

Table 3 Continued.

Treatment	Author	LOE	Diagnosis (no. of patients)	Study type	No. of patients (age)
Retinoids					
Etretinate	Kim *et al.*[22]	4	EP (3)	OL	3 (10-12 y)
Etretinate	Van der Rhee *et al.*[21]	4	PP (2)	CS	2 (8 y)
Cyclosporine					
Cyclosporine A	Kilic *et al.*[35]	4	GPP (3)	CS	3 (10 mo – 6 y)
Cyclosporine	Alli *et al.*[36]	5	GPP (1)	CR	1 (9 y)
Cyclosporine	Torchia *et al.*[37]	5	Photosensitive psoriasis (1)	CR	1 (15 y)
Cyclosporine	Mahe *et al.*[38]	4	PPP (1); EP (1); PP (1); GPP (1)	CS	4 (2-10 y)
FAE					
FAE	Balak *et al.*[44]	2b	PP (11); PP + GP (2); PP + PPP (1)	RCS	14 (8- 17 y)
FAE	Gerdes *et al.*[45]	5	PP (1)	CR	1 (11 y)
FAE	Steeman *et al.*[46]	5	NS (1)	CR	1 (15 y)
FAE	Günther *et al.*[43]	5	PP (1)	CR	1 (14 y)

	Dose regimen	Duration of treatment	Outcome	Safety
	0.5-0.9 mg/kg/d	4-5 mo	Clearance erythema and scaling: 100%	Cheilitis (3), skin fragility, hair loss and pruritus described in whole cohort
	25 mg/d (maintenance 12.5 mg/d)	13-17 mo	Excellent: 100%	Moderate cheilitis (1)
	1-2 mg/kg/d	12, 6, 5 mo	Almost completely disappeared: 33%; Completely disappeared 66%	No side effects
	3 mg/ kg/d	11 mo; 2 wk to control	Free of psoriasis: 100%	n.m.
	3.5 mg/kg/d	3 wk	Lesions healed: 100%	n.m.
	2.5-10 mg/kg/d	3.5-6 mo	No response: 100%	n.m.
	Highest daily dose:			
	120-720 mg/d	1-80 mo (median 10 mo)	Complete clearance: 36% (5/14); good improvement (PASI 82): 7% (1/14); partial response: 21% (3/14); non-response: (5/14) 36% including increase in PASI in 2 patients (27% and 31% increase resp.)	Abdominal cramps (5); diarrhea (4); flushes (2); nausea (1); bronchitis (1); fatigue (1); elevated liver function- tests (3); mild temporary shifts in leukocyte counts (3); mild increase in serum creatinine level (1); transient mild proteinuria (+1) (1)
	480 mg/d (maintenance dose120- 240 mg/d)	3 y	PASI 20.2 → 0.8 (3 mo) BSA 20% → 1% (3 mo)	Abdominal discomfort and flushes; reduction of lymphocytes
	480 mg/d; maintenance dose 120-240 mg/d)	20 mo	Clearance: 100%	Abdominal cramps (1)
	240mg/d	-	PASI 19.7 → 1 (16 wk)	Reversible lymphopenia

Table 3 Continued.

Treatment	Author	LOE	Diagnosis (no. of patients)	Study type	No. of patients (age)
MTX					
MTX	Collin *et al.*[47]	4	PP (11), Suberytrodermic (2)	RCS	13 (5-16 y)
MTX	Kaur *et al.*[48]	4	PPP (1); EP (3); PP (17); GPP (3)	RCS	24 (2-14 y)
MTX	Kumar *et al.*[49]	4	EP (3); PP (2); GPP (2)	RCS	7 (3-16 y)
MTX	Juanqin *et al.*[16]	4	GPP (4)	RCS	4 (2-12 y)
MTX	Kalla and Goyal.[50]	5	GPP (1)	CR	1 (4 y)
MTX	Dogra *et al.*[52]	5	GPP (1)	CR	1 (2 y)
MTX	Dogra *et al.*[51]	5	GPP (1)	CR	1 (4 y)
MTX	Ivker *et al.*[53]	5	GPP (1)	CR	1 (3 mo)
Biologics					
Adalimumab	Alvarez *et al.*[82]	5	GPP (1)	CR	1 (13 y)
Adalimumab	Dini *et al.*[83]	5	ACH (1)	CR	1 (9 y)
Etanercept	Beikert *et al.*[69]	4	PP (4) EP (4)	RCS	8 (7-16 y)

	Dose regimen	Duration of treatment	Outcome	Safety
	0.03-0.41 mg/kg/wk	2-267 wk (mean 71 wk)	Good response: 10 (76.9%); moderate response: 1 (7.7%); poor response: 1 (7.7%).	Raised liver enzymes (9), gastro-intestinal symptoms (6), mouth ulcers and easy bruising (1), transient nocturnal cough and leg pains (1)
	0.2-0.4 mg/kg/wk	2-16 mo (mean 4.97)	PASI 75: 91.7%; PASI 50-75: 8.3%	Nausea, vomiting, and loss of appetite: 9/24 (37.5%)
	0.2-0.4 mg/kg/wk	6-10 wk to control (mean 7.9): duration 31.2-46.4 wk (mean 38.8)	>75% Clearance: 100%	Nausea and vomiting 3/7 (42.9%).
	0.2-0.4 mg/kg/wk	-	>80% Clearance: 100%	n.m.
	0.2 mg/kg/wk	≥10 wk	Marked improvement: 100%	n.m.
	0.4 mg/kg/wk	-	Clearance of pustules: 100%	No side effects
	0.3 mg/kg/wk	12 wk	Almost complete remission: 100%	No side effects
	0.3 -0.5 mg/kg/wk im	4 wk	Clearing: 100%	n.m.
	40 mg sc week 0, 1; thereafter every 2 wk	15 mo	BSA >90% (8 wk); clearance (16 wk)	n.m.
	80 mg sc week 0; 40 mg wk 1; thereafter 40 mg every 2 wk	12 mo	PP- PASI 62 → 6 (4 wk); Complete resolution of clinical aspects (8 wk)	No adverse events
	0.8 mg/kg/wk	5-16 mo (median 11 mo)	PASI-75: 75% (12 wk)	Injection site reaction n = 2

Table 3 Continued.

Treatment	Author	LOE	Diagnosis (no. of patients)	Study type	No. of patients (age)
Biologics					
Etanercept	Fabrizi *et al.*[63]	5	EP (1)	CR	1 (22 mo)
Etanercept	Farnsworth *et al.*[66]	5	PP (1)	CR	1 (14 y)
Etanercept	Fotiadou *et al.*[79]	5	PP (1)	CR	1 (14 y)
Etanercept	Hoang and Burruss.[62]	5	PP (1)	CR	1 (14 y)
Etanercept	Kress *et al.*[67]	4	PP (3)	CS	3 (9-18 y)
Etanercept	Mazzotta *et al.*[73]	5	PPP (1)	CR	1 (11 y)
Etanercept	Paller *et al.*[61]	1b	PP (211); treated (106), placebo (105)	RCT	211 (4-17 y)
	Siegfried et al.[78]		*PP (138); treated (69), placebo (69)*		*138 (4-17 y)*

	Dose regimen	Duration of treatment	Outcome	Safety
	0.4 mg/kg b.i.w., ≥ 12 wk once weekly	6 mo	At week 12: PASI 37 → 1.2 BSA 80% → 7%	No considerable side effects
	25 mg b.i.w.	8 mo	No improvement:100%	Without side effects
	0.8 mg/kg/wk	16 wk	PASI 18 → 15.8 (16 wk)	n.m.
	25 mg b.i.w.	8 mo	Clearance of all lesions except those plaques on elbows and knees: 100%	Localized cutaneous Cryptococcus albidus infection scalp
	0.4 mg/kg b.i.w. (<50 kg) or max 50 mg/wk	27; 27; 30 mo	PGA almost clear: 100%	Injection site reaction n = 1 in whole cohort
	0.4 mg/kg b.i.w.	1) 48 wk 2) 288 wk	1) PASI 25.8 → 0 (12 wk); 0 (48 wk) 2) PASI 21.7 → 1.2 (12 wk); 0 (48 wk); 0 (288 wk)	Adverse events have not been noticed or reported
	0.8 mg/kg/wk, max 50 mg	48 wk; 12 double blinded, 24 open label etanercept, 12 double blinded	Week 12 PASI 90: 27%; PASI 75: 57%; PASI 50: 75%; Mean improvement in PASI: 68%; PGA (almost) clear: 53% Week 24: PASI 75: 69%; Mean improvement in PASI: 77%; PGA (almost) clear: 57% Week 36: PASI 75: 68%; Mean improvement in PASI: 77%; PGA (almost) clear: 53%	Non-infectious AEs: 287.6 per 100 patient-years Infections: 229.3 per 100 patient-years Total AEs: 554.5 per 100 patient-years No SAEs up to wk 12. Wk 12-36: Removal of ovarian cyst (1) Concurrent infectious gastroenteritis and associated dehydration (1) Basilar pneumonia (1)
		12 wk (after 12 wk double blinded, 24 open label ETN)	*ETN group:* *Week 48:* *PASI 75: 80%* *PGA (almost) clear: 58%*	*No SAEs, no serious infections*

Table 3 Continued.

Treatment **Biologics**	Author	LOE	Diagnosis (no. of patients)	Study type	No. of patients (age)
	Paller et al.[75]		*PP (182)*		*182 (4-17 y)*
Etanercept	Papoutsaki *et al.*[64]	4	PP (2) PPP (1) GPP and EP (1)	CS	4 (6-15 y)
Etanercept	Ruiz *et al.*[77]	4	PP (3)	RCS	3 (3-12 y)
Etanercept	Sachdev *et al.*[80]	5	PP (1)	CR	1 (14 y)
Etanercept	Safa *et al.*[65]	5	EP (1)	CR	1 (7 y)
Infliximab	Farnsworth *et al.*[66]	5	PP (1)	CR	1 (14 y)
Infliximab	Menter and Cush.[88]	5	PP and PPP (1)	CR	1 (13 y)
Infliximab	Pereira *et al.* [87]	5	GPP (1)	CR	1 (3 y)
Infliximab	Weishaupt *et al.*[86]	5	GPP (1)	CR	1 (16 y)
Ustekinumab	Dixit *et al.*[85]	5	PP (1)	CR	1 (16 y)
Ustekinumab	Fotiadou *et al.*[79]	5	PP (1)	CR	1 (14 y)
Colchicine	Zachariae *et al.*[97]	5	GPP (1)	OL	1 (12 y)
Colchicine	Wahba and Cohen.[98]	5	GP and PP (1)	OL	1 (4 y)

ACH, acrodermatitis continua of hallopeau; AEs, adverse events; b.i.d., two times a day; b.i.w., twice weekly; BSA, body surface area; CR, case report; CS, case series; d, days; EP, erythrodermic psoriasis; ETN, etanercept; FAE, fumaric acid esters; GP, guttate psoriasis; GPP, pustular psoriasis; im, intramuscular; LOE, level of evidence; mo, months; MTX, methotrexate; n.m., not mentioned; NS, not specified; OL, open-label trial; PASI, Psoriasis Area and

Dose regimen	Duration of treatment	Outcome	Safety
	96 wk (open label extension after 48 wk RCT)	*PASI 90: 30%; PASI 75: 61%; PASI 50: 89%; Mean improvement in PASI: 75.4%; PGA (almost) clear: 47%*	*5 SAEs not considered to be related to ETN 80.1% (n= 145) one or more AE.*
0.4 mg/kg b.i.w.	24-86+ wk	PASI 25.8 → 0 (GPP and EP); PASI 21.2 → 0 (PP); PASI 27.4 → 5.9 (PP); PASI 9.2 → 2.2 (PPP)	No adverse events
25 mg/wk	1 y	PASI 75: 100%	Mild injection site reaction
50 mg/wk	8 mo	Almost cleared: 100%	< 12-48 hours headache, fever, neutropenia
0.4 mg/kg, b.i.w.	≥ 6 mo	Significant clinical improvement: 100%	Treatment was well tolerated without any adverse reactions.
5 mg/kg	≥ 6 wk	Marked clearing of psoriasis: 100%	Without complications
3.3 mg/kg	≥ 30 wk	Trunk and limb plaques cleared, with significant improvement of palmoplantar disease: 100%	Without side effects
5 mg/kg	10 mo	Completely clear: 100% in 2 wk, after 13 wk flare, after 10 mo insufficient effect	No adverse events
5 mg/kg	1 administration	Pustules resolved, erythema lightened: 100%	Neither patient experienced adverse drug effects
90 mg	18 mo	PASI 100: 100% (PASI 21.2 → 0 at week 8)	No side effects
45 mg	1y	PASI 90: 100% at week 16; PASI 100 at 1y (PASI 15.8 → 0 at 1y)	No adverse events
0.5 mg b.i.d.	-	Symptoms disappeared: 100%	Mild abdominal discomfort (1) in whole cohort
0.25 mg t.i.d.	2 mo	Excellent: 100%	Mild gastrointestinal symptoms in whole cohort

Severity Index; PGA, Physician Global Assessment; PP, plaque psoriasis; PPP, palmoplantar psoriasis; PP-PASI, Palmoplantar Pustular Psoriasis Area and Severity Index; RCS, retrospectively reviewed case series; RCT, randomized controlled trial; SAEs, serious adverse events; sc, subcutaneous; t.i.d., three times a day; wk, weeks; y, years; -, unknown; *italicized,* same cohort described in the original study from Paller *et al.*, 2008[61].

Cyclosporine

In former review four studies[35-38] were included, based on which cyclosporine treatment was considered to be ambiguous. Description of safety profiles was rare.[4] In the present review four new studies[39-42] were found. All were excluded because of the use of systemic antipsoriatic combination therapy[39] (*n* = 1), unclear outcome measure (*n* = 1)[40] and a combination of these (*n* = 2).[41,42]

Conclusion

Grade C.

Number of patients treated with cyclosporine: 9.

As a new recommendation with respect to the use of cyclosporine in the treatment of pediatric psoriasis cannot be made, the described efficacy of cyclosporine treatment still remains ambiguous. Safety issues were sparsely described.[4]

Fumaric acid esters (fumarates)

In the former review, fumaric acid esters (FAE) were not described, as at that time only one case report existed.[43] Between 2008 and 2014 three new studies[44-46] were published. All four articles were included: three case reports (LOE5)[43,45,46] and one case series (LOE2b).[44] In two case reports, more than 90% improvement in Psoriasis Area and Severity Index (PASI) was achieved after 16 weeks[43] and 3 months[45] respectively. In one patient FAE were continued for more than 3 years.[45] Another case report described 100% clearance after 3 months.[46] The retrospective case series[44] of 14 children denotes complete clearance in 36% of patients, good improvement (more than 80% in PASI) in 7%, partial response in 21% and non-response in 36%. FAE were given in a starting dose of dimethylfumarate 30 mg, with an incremental increase up to a maximum daily dosage of 720 mg based on clinical response and tolerability.[44] Duration of treatment was up to 80 months (median 10 months).[44]

Abdominal cramps, diarrhea, transient shifts in leukocyte counts, temporary elevated liver function tests and flushes were the most frequently reported side effects.[43-46] Mild increase in the serum creatinine level was reported in one patient[44] and transient mild proteinuria in another patient.[44]

Conclusion

Grade C.

Number of patients treated with FAE: 17.

FAE are effective in a subgroup of patients with the main side effects being gastrointestinal complaints, transient shifts in leukocyte counts, transient elevated liver function tests and flushes.

Methotrexate

Former review included eight studies,[16,47-53] based on which MTX was considered to be effective in moderate to severe pediatric psoriasis. Mild to severe nausea and vomiting were the most frequently reported side effects.[4]

In our search nine[31,33,54-60] new publications were found. All studies were excluded; because of an unclear treatment regimen ($n = 1$),[54] a combination of an unclear treatment regimen and an unclear outcome measure ($n = 1$),[55] no separate data available on pediatric psoriasis ($n = 1$),[57] and systemic combination therapy ($n = 6$).[31,33,56,58-60]

Conclusion

Grade C.

Number of patients treated with MTX: 52.

As no new evidence on efficacy and safety of MTX in pediatric psoriasis could be added, MTX still seems to be an effective treatment option in moderate to severe pediatric psoriasis with a reasonable safety profile. Most evidence is available for plaque-type psoriasis.[4]

Biologics

Etanercept

Based on the former seven included studies,[61-67] etanercept was concluded to be an effective treatment in plaque-type psoriasis with infections being the most common short-term side effects.[4] Fourteen new studies were found.[60,68-80] Seven studies were exluded,[60,68,70-72,74,76] because of an unclear outcome measure and/or systemic combination therapy ($n = 4$),[60,68,70,74] subgroup analyses of an original double-blind randomized controlled trial (RCT)[61] which was already mentioned in our previous review[4] ($n = 2$),[72,76] and only quality of life (QoL) outcomes of the same previously mentioned cohort ($n = 1$).[71]

In the present review, new publications on the cohort described in the 48-week phase III double-blind RCT (LOE1b)[61] were included, containing long-term data.[75,78] At week 48 and 96 PASI 75 was achieved in 80% and 61% of patients respectively.[75,78]

In a retrospective case series (LOE4) in eight children PASI 75 was achieved in 75% at week 12.[69] In another case series[77] and two case reports,[73,80] all patients achieved at least 75% improvement in PASI. In one 14-year-old boy with plaque-type psoriasis PASI decreased from 18 to 15.8 after 16 weeks.[79]

During the open-label part of the above mentioned RCT, four serious adverse events (SAEs) occurred in three patients including three infections; all resolved without sequelae.[61] During 96 weeks of follow-up, three patients (1.7%) reported five SAEs: anxiety (n = 1), postoperative intestinal obstruction (n = 1), dehydration, abdominal pain, hospital admission and subsequently abortion (n = 1).[75] None were considered to be related to etanercept.[75] Opportunistic infections, malignancies or deaths were not reported.[75] In total 145 patients (80.1%) reported one or more adverse event (AE), mostly infections.[75]

Ten patients (5.5%) reported injection site reactions.[75] Mild injection site reactions were also reported in two other studies.[69,77] In one case report a rapid-onset neutropenia was described within 48 h after etanercept injection; subsequent rechallenge after 1 month was well tolerated without side effects.[80]

Conclusion

Grade A.

Number of patients treated with etanercept: 236.

Etanercept is an effective biologic in the treatment of pediatric plaque-type psoriasis. The most common reported short-term side effects are infections.[4] In a 96-week follow-up period, etanercept shows a large efficacy and reassuring safety profile. Long-term safety profiles are not available.

Adalimumab

In 2005, one case report described an adolescent girl with recalcitrant GPP treated with a combination of adalimumab, methotrexate and cyclosporine.[81] This study was excluded because of systemic combination therapy. Current literature search revealed three new studies.[82-84] One study was excluded because separate data on pediatric psoriasis were not available.[84] In a 13-year-old girl with GPP, more than 90% improvement in body surface area (BSA) was achieved after 8 weeks, with clearance after 16 weeks using adalimumab 40 mg at week 0, 1 and every 2 weeks thereafter. Safety data were not available (LOE5).[82] In another case report (LOE5) describing a 9-year old girl with acrodermatitis continua of hallopeau (ACH), complete resolution of clinical aspects was achieved after 8 weeks with adalimumab; adverse events did not occur.[83]

Conclusion

Grade D.

Number of patients treated with adalimumab: 2.

A solid conclusion on efficacy and safety of adalimumab could not be drawn on two patients.

Ustekinumab

Up to September 2008, evidence on the use of ustekinumab in the treatment of pediatric psoriasis was lacking.[4] Nowadays, two new case reports (LOE5) were identified.[79,85] Ustekinumab was used in two children with plaque psoriasis in a dosage of 90 mg[85] and 45 mg[79], respectively; injections were administered at week 0 and 4 and every 12 weeks thereafter. Both patients responded very well with more than 90% improvement in PASI at week16[79] and 100% improvement at week 8 respectively.[85] Adverse events did not occur.

Conclusion

Grade D.

Number of patients treated with ustekinumab: 2.

Due to the low number of patients, a solid conclusion on efficacy and safety of ustekinumab could not be drawn.

Infliximab

The use of infliximab in pediatric psoriasis was already described in four cases in the former review (LOE5).[66,86-88] Currently, two new studies were identified.[27,59] Both were excluded because of systemic antipsoriatic combination therapy.

Conclusion

Grade D.

Number of patients treated with infliximab: 4.

As no new evidence could be added to our previous review, a solid conclusion with respect to infliximab in the treatment of pediatric psoriasis could not be drawn.

Other systemic therapies

One new study on the use of dapsone was excluded[89] due to an unclear outcome measure. In addition, literature search revealed one new study on thalidomide[90] but this study was excluded due to the combination with ultraviolet B radiation therapy. One case report describing an infant with GPP treated with anakinra was excluded as this child had an interleukin-36-receptor antagonist deficiency.[91]

Discussion

In daily clinical practice, the management of moderate to severe pediatric psoriasis is intriguing and challenging.[9,10] Several issues will influence the choice of (systemic) treatment e.g. age, disease severity, previous treatments, level of disability (the influence on QoL), presence of comorbidities, practicality of the regimen, costs, accessibility and patient preferences.[6,8,9,12]

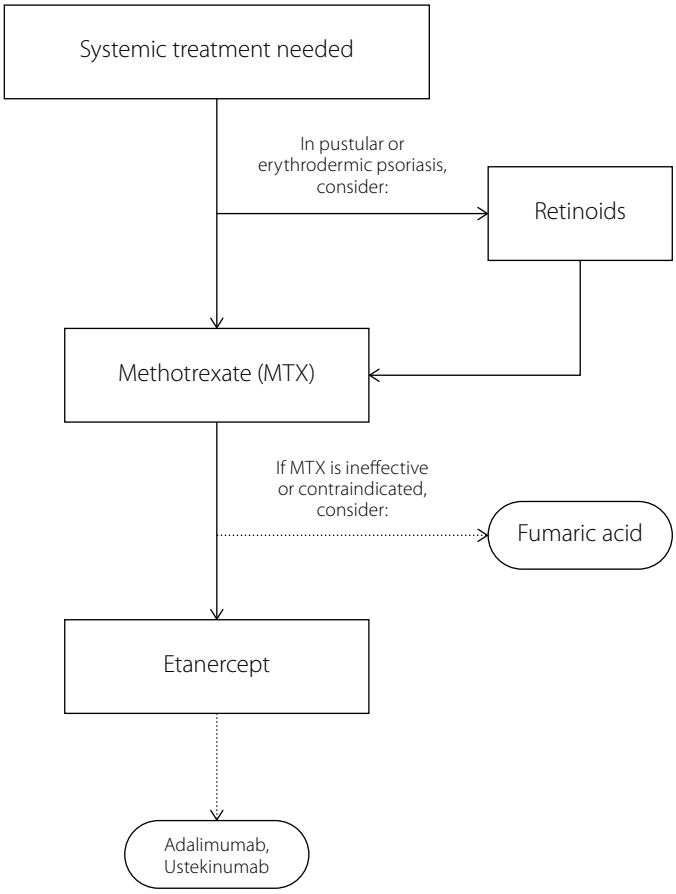

Figure 1 Treatment algorithm.

Although these aspects will differ for each child and also between countries, the benefits and risks of a treatment and especially the long-term health risks of medication or inadequate treatment are a general concern for all dermatologists treating children with psoriasis.[6] It is therefore very important to make the decisions based on the available evidence. In this review, the evidence on systemic treatments in pediatric psoriasis is updated until March 2014.

Based on the present review, we suggest the following adapted treatment algorithm (Figure 1) for children who need to be treated with systemic agents. MTX is still considered to be the first systemic treatment of choice with most data available on plaque-type psoriasis.[4] Although the body of evidence of MTX has not increased, and is only retrospec-

tively collected, it is still the most extensive of the conventional systemic treatments and is found to be effective. Side effects most frequently reported in the pediatric psoriasis literature are nausea, vomiting and transient elevation of liver enzymes.[4,47-49] In addition to the evidence found in the pediatric psoriasis literature, MTX has been used for a long time and has a track record of well-tolerated and effective use in juvenile idiopathic arthritis (JIA) literature.[92] Based on the evidence presented in this review in combination with the long-term safety aspects of MTX in JIA, we recommend this conventional systemic treatment as preferred before use of other systemic treatments.

The evidence on the efficacy and safety of retinoids is still mainly shown in pustular and erythrodermic psoriasis with the majority of data describing etretinate. In those subtypes, it is an effective treatment with frequently reported side effects. Up to now, the efficacy of cyclosporine treatment in pediatric psoriasis remains ambiguous and a solid conclusion could not be drawn.

In case of plaque-type psoriasis and ineffectiveness or contraindication for MTX, FAE could be considered in a subgroup of patients. Based on the limited new evidence available on induction therapy, fumarates have shown to be reasonably effective and safe in a subgroup of pediatric patients. To date, prospective studies are not available, but are currently being performed.[13] As up to now, the evidence on FAE is limited, and only retrospectively collected, we placed this agent with a dotted line in the treatment algorithm.

Etanercept is shown to be effective and has still accumulated most evidence of all available systemic treatments, with a large efficacy and reassuring safety profile in a 96-week follow-up.[75] In JIA, 8 years of continuous etanercept seems well tolerated with a rate of serious infections at 0.03 per patient-year.[93] The promising efficacy of biologics, however, needs to be balanced against the relative lack of long-term safety data and high costs.[8,9] In addition, an increased risk of lymphoma and other malignancies in children and adolescents with arthritis, inflammatory bowel disease or sarcoidosis treated with tumour necrosis factor-α (TNF-α) blokkers is speculated.[6,94] However, it has to be taken into account that the majority of patients also used other immunosupressives and the contribution of the underlying disease states on the risk of malignancy could not be assessed.[6,94] To date, the Food and Drug Administration (FDA) concluded that it is unable to fully characterize the strength of the association between the use of TNF blockers and development of malignancy.[6,94] Therefore, we still consider etanercept a third-line drug in severe and/or recalcitrant psoriasis when the conventional systemic treatments are ineffective, contraindicated or discontinued because of adverse events. In the future, when sufficient long-term safety data are collected, etanercept will probably get a more prominent position in the treatment algorithm. In the present review, a solid conclusion on the use of adalimumab and ustekinumab could not be drawn due to the low number of patients. At the moment, there are two ongoing Phase III multicenter RCTs evaluating the use of ustekinumab and adalimumab in pediatric psoriasis respectively.[95,96] Therefore, we placed them with a dotted line in Figure 1.

In conclusion, there is still limited evidence on the efficacy and safety of systemic treatments in pediatric psoriasis and there is especially a lack of long-term safety data. Therefore, there is a compelling need for a prospective, multicenter, international registry on systemic treatments in pediatric psoriasis to investigate in a consequent and standardized manner the effectiveness and safety of systemic treatments in this vulnerable age group.

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2.3

Methotrexate in pediatric plaque-type psoriasis: long-term daily clinical practice results from the Child-CAPTURE registry

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Abstract

Background: Evidence on effectiveness and safety of methotrexate (MTX) in pediatric psoriasis is scarce.

Objectives: To study the effectiveness and safety of MTX in pediatric plaque-type psoriasis and its influence on quality of life (QoL) in daily clinical practice.

Methods: Subset analysis of prospectively collected data extracted from the Child-CAPTURE registry, a single center, longitudinal, long-term, observational daily practice cohort of pediatric psoriasis patients. A maximum dose between 0.14 and 0.63 mg/kg once weekly was prescribed in 25 children. Primary endpoints were percentages of patients with ≥75% improvement in the Psoriasis Area and Severity Index (PASI) at week 12 and 24.

Results: PASI 75 was achieved in 4.3% and 33.3% of patients at week 12 and 24, whereas 40% and 28.6% reached PASI 75 at week 36 and 48. Median PASI and body surface area decreased from 10.0 (range 3.8-42.4) and 11.0 (range 3.5-72.0) at baseline to 4.3 (range 0-19.8) and 2.6 (range 0.0-39.6) at week 24, respectively. Physician Global Assessment improved significantly from 3.0 to 1.2 at week 24. A significant decrease in Children's Dermatology Life Quality Index from 9.0 to 3.8 at week 24 was found. Most reported adverse events were severe nausea (n = 5), infections requiring antibiotics (n = 5) and tiredness (n = 4).

Conclusions: MTX shows a positive effect on PASI scores, improves QoL and has a reasonable safety profile.

Introduction

In 30% of patients with psoriasis, the onset of disease is before adulthood.[1] Pediatric psoriasis has a negative impact on the quality of life (QoL), self-esteem and psychosocial development.[2] Methotrexate (MTX) is a well-known systemic treatment for moderate to severe pediatric psoriasis[3]; however, evidence on its effectiveness and safety is scarce, and prospective data are not available. Until now, three retrospective case series on MTX in pediatric plaque-type psoriasis were published.[4-6] Only one study used the Psoriasis Area and Severity Index (PASI) as an objective treatment outcome measure [4] and neither study evaluated the influence on the QoL or the drug survival. For a balanced positioning of MTX in the systemic treatments of pediatric psoriasis, prospective evidence is of major importance.

This study aims to evaluate the effectiveness of MTX in the treatment of pediatric plaque-type psoriasis by means of data extraction from the existing Child-CAPTURE registry (Continuous Assessment of Psoriasis Treatment Use Registry), a prospective, long-term, longitudinal, observational daily practice cohort of pediatric patients with psoriasis. In addition, safety data, the influence on QoL and the 48-and 96-week drug survival of MTX were evaluated. In sub-analysis, we investigated the influence of body mass index (BMI) and waist circumference (WC) on the effectiveness of MTX.

Patients and methods

Study design

This study was a subset analysis of a single-group, prospective, observational, daily clinical practice cohort enrolling children with moderate to severe plaque-type psoriasis treated with MTX. This study has been carried out in the Netherlands in accordance with the applicable rules concerning the review of research ethics committees and informed consent.

Study population

Data were prospectively collected using the Child-CAPTURE, a prospective, longitudinal, long-term, observational, daily practice pediatric psoriasis registry. The Child-CAPTURE was set up in September 2008 to monitor the effectiveness, safety of treatments and QoL in all pediatric psoriasis patients (≤ 18 years old) visiting the outpatient clinic of the Department of Dermatology at the Radboud university medical center.[7] At baseline, patient and treatment characteristics were prospectively collected in the Child-CAPTURE using a standard case record form including: age, sex, age of onset, family history of psoriasis, presence of psoriatic arthritis, medical history, present and previous antipsoriatic treatments and concomitant non-dermatological medication. At each visit, disease

severity scores (PASI; Physician Global Assessment, PGA; and body surface area, BSA) were recorded for every child. In addition, physical parameters (body height, weight and WC), Children's Dermatology Life Quality Index (CDLQI) and the occurrence of (serious) adverse events (AEs) were noted. In this study, a subset analysis was performed on all pediatric plaque-type psoriasis patients (age <18 years) treated with MTX for their psoriasis at our outpatient clinic between September 2008 and December 2013.

Children were treated with MTX if they failed to respond to topical corticosteroids and/or dithranol, and/or UVB phototherapy (if adolescent). MTX was prescribed if PASI and/or CDLQI were 10 or higher. If any of the following PASI, BSA and CDLQI were ≥ 7 and < 10, and in addition the areas that were affected were more likely to have functional or psychosocial impact, these patients were included.

Exclusion criteria were: age ≥ 18 years, the use of MTX at the first visit, pustular, guttate or erythrodermic psoriasis, concomittent antipsoriatic treatment other than topical treatment and the presence of a contraindication for treatment with MTX.[8]

Protocol

Before commencing MTX, screening laboratory tests were conducted including hematological analysis, serum chemistry, hepatitis B and C serology and in females of childbearing potential, a pregnancy test. The proposed MTX starting dose was an oral dose of 0.2-0.4 mg/kg once a week followed by folic acid 5 mg once weekly[9], 24 hours later. However, the MTX starting dose never exceeded 20 mg/week. The oral tabs were taken all at once. Visits were scheduled at week 6 and 12 and every 12 weeks thereafter. Routine laboratory tests were conducted at week 1 (before the second intake of MTX), week 3, 6, 9 and 12 and every 12 weeks thereafter. Patients and parents were instructed to interrupt MTX in case of fever, illness or malaise. Patients were allowed to use topical therapies on all areas of the body according to their own discretion. According to the daily clinical practice design, no wash-out period was performed.

Outcome measures

The PASI (score 0-72) and the percentage of affected BSA (score 0-100) were used to measure the extent and the severity of psoriasis.[10] PASI 50, PASI 75, and PASI 90 were calculated. These measures denote improvements in the PASI of 50%, 75% and 90% relative to baseline, respectively. The PGA was used to assess the overall severity of psoriasis graded from 0 to 5 (0 indicates clear and 5 very severe).

A validated Dutch version of the CDLQI was used (10 items; score 0-30) to quantify the impact of psoriasis. More impairment in QoL is indicated by higher scores in CDLQI.[11,12] AEs of interest and serious adverse events (SAEs) were recorded. The AEs of special interest were: nausea and/or other gastrointestinal complaints, tiredness, laboratory abnormalities (all requiring adjustment of treatment regimen), infections requiring medication to resolve, bone marrow suppression and malignancies. Multiple occurrence of identical AE in a

single subject were counted once. SAE was defined as an event that resulted in death, was life threatening, required inpatient or prolonged hospitalization or resulted in persistent or significant disability or incapacity. BMI was calculated as weight in kilograms divided by height in meters squared.[13] An age- and sex-adjusted BMI was assigned[14] with cutoffs for overweight and obesity. WC was measured midway between the lowest rib and the superior border of the iliac crest with an inelastic measuring tape.[13,15] An age- and sex-adjusted WC was determined based on a cutoff > 1.3 SDS for overweight and > 2.3 SDS to detect obesity in Dutch children.[15]

Endpoints

Primary endpoints included PASI 75 at week 12 and 24. Secondary endpoints included PASI 50 and PASI 90 at week 12 and 24, PGA/BSA reduction, improvement in QoL, evaluation of the effectiveness at week 36 and 48 as well as safety data. In addition, the influences of BMI and WC on the effectiveness of MTX and 48-and 96-week drug survival times and reasons for discontinuation were analysed. Drug survival is the amount of time a patient remains on a specific treatment.[16,17]

Statistical methods

PASI, BSA, PGA and CDLQI were analysed for a 48-week period and were interpolated to obtain outcome measures at week four and every four weeks thereafter. Effectiveness analysis using PASI and BSA were performed in two ways: (1) according to an as-treated principle and (2) intention-to- treat analysis using last observation carried forward (LOCF) until 48 weeks in patients who discontinued MTX treatment.[18] End of the treatment episode was defined as a discontinuation of MTX therapy during 12 weeks or more.

A linear mixed model for repeated measurements was used to study the influence of age at start of MTX, BMI, WC, age-and sex-adjusted BMI, age-and sex-adjusted WC and subcutaneous administration on the effectiveness of MTX, separately. The dependent variable was PASI. The independent continuous variables were age at start of MTX (BMI, WC, age-and sex-adjusted BMI, age-and sex-adjusted WC and subcutaneous administration, respectively), time since start of treatment and the baseline PASI value. Initially, also all first-order interaction terms with time were included in the linear part of the model, but these terms were removed from the final model because these did significantly improve the fit to the data. Furthermore, the intercept of each patient was treated as a random variable. This allows different levels for different patients.

The Wilcoxon signed-rank test was used to test the change since baseline of the outcomes at weeks 12, 24, 36, and 48, respectively, for statistical significance. The Kaplan-Meier method was used to study the time to MTX discontinuation and the estimate 48- and 96- week drug survival of MTX with the 95% confidence interval (CI) are presented.

p Values <0.05 (two-sided) were considered statistically significant. The statistical analyses were performed using SPSS® version 20.0 for Windows® (SPSS Inc., Chicago, IL),

SAS® version 9.2 for Windows® (SAS Institute Inc., Cary, NC) and Microsoft Office Excel 2007 SP3 MSO (Microsoft Corporation, Redmond, WA).

Results

Patient characteristics

Twenty-five children (52% male) were included. In total, six patients (24%) used MTX subcutaneously. Five patients switched from oral MTX to subcutaneous administration because of ineffectiveness of oral MTX tabs ($n = 3$), nausea ($n = 1$) and active arthritis ($n = 1$). One patient directly started with subcutaneous administration of MTX because of nausea during a previous treatment episode with MTX, which was before foundation of our registry. Median time of switching from oral to subcutaneous administration ($n = 5$) was 37.1 weeks (range 13.0-88.3).

Most patients were treated with dithranol any time before commencing MTX, but in the three months prior to start of MTX, 14 patients (56%) used systemic therapy and/or UVB phototherapy and/or dithranol (Table 1). The median start dose of MTX was 15 mg once weekly with a maximum start dose of 20 mg once weekly, based on the weight of the patient. In 12 children, initial MTX dosages were increased between week 6.7 and week 31.3 (median 14.4) until a maximum dose of 25 mg once weekly. In four of these 12 patients, dosage was tapered. In addition, in four other children dosage was also tapered.

The median BMI of the children in our study was 21.2 (range 13.4-35.3). Of the 25 children, 32% ($n = 8$) had an age-and sex-adjusted BMI above the normal range (overweight 32%; obesity 24%). Of the 24 children of which a WC was available, 33.3% had an age-and sex-adjusted WC above the normal range (overweight 33.3%; obesity 20.8%). At week 12, 24, 36 and 48, the number of patients was 23 (92%), 21 (84%), 15 (60%) and 14 (56%), respectively, compared with 25 patients (100%) at baseline (Table 2).

Effectiveness

As treated analysis

PASI 75 was reached in 4.3%, 33.3%, 40% and 28.6% of patients after 12, 24, 36 and 48 weeks. Rates of PASI 50 were 39.1%, 66.7%, 80% and 71.4% at week 12, 24, 36 and 48; PASI 90 was achieved in 0%, 23.8%, 20% and 14.3%, respectively (Figure 1). Median PASI at baseline was 10.0 (range 3.8-42.4) compared with 5.8 (range 2.4-30.0), 4.3 (0-19.8), 3.6 (0-8.4) and 3.4 (0-11.8) at weeks 12, 24, 36 and 48, respectively (Table 2). BSA values at weeks 12, 24, 36, and 48 and percentage of improvement are described in Table 2 and Figure 1.

LOCF analysis

PASI 75 was reached in 4%, 32%, 40% and 32% of patients after 12, 24, 36 and 48 weeks. Rates of PASI 50 were 40%, 64%, 72% and 68% at week 12, 24, 36 and 48; PASI 90 was

Table 1 The characteristics of the children with plaque-type psoriasis ($n = 25$) in this study.

Patient characteristics	median (range)/ *n* (%)
Age (years) at start MTX	15.0 (6-17)
Age (years) onset psoriasis	9.0 (0-16)
Baseline PASI	10.0 (3.8-42.4)
Duration MTX therapy (weeks)	60.4 (12.6-163.4)
Cumulative dose (mg)	793 (165-2725)
BMI (kg/m^2)	21.2 (13.4-35.3)
Age-and sex-adjusted BMI above the normal range	8 (32)
Waist circumference (cm)	71 (51-132)
Age-and sex-adjusted WC above the normal range	8 (33.3)
Male gender	13 (52)
Psoriatic arthritis	3 (12)
Subcutaneous use	6 (24)
Previous therapies	
Potent topical corticosteroids	25 (100)
Dithranol	19 (76)
Phototherapy	18 (72)
Fumaric acid	3 (12)
Cyclosporine	1 (4)
Retinoids[a]	1 (4)
Etanercept[b]	1 (4)

MTX, methotrexate; PASI, Psoriasis Area and Severity Index; BMI, body mass index; WC, waist circumference;
[a] For five days.
[b] Single injection.

achieved in 0%, 20%, 24% and 20%, respectively (Figure 1). Median PASI compared with baseline was similar to the results of the as treated analysis. Note that in this figure, the results following the principles of intention-to treat (LOCF) show much smoother lines compared with the as treated analysis. Moreover, these fluctuations are absent with respect to the medians in Table 2 for either analysis. Therefore, fluctuations in the as treated analysis are strongly related to drop-outs.

PGA

At week 12, 24, 36 and 48, median PGA was significantly lower compared with baseline (Table 2). PGA decreased from 3.0 at baseline to 2.1 and 1.2 at week 12 and 24, respectively.

Table 2 The observed and change since baseline of Psoriasis Area and Severity Index (PASI), body surface area (BSA), Physician Global Assessment (PGA) and total Children's Dermatology Life Quality Index (CDLQI) of the children with plaque-type psoriasis treated with MTX.

Outcome	Weeks since baseline	No. of patients	Observed	Change since baseline	
			Median (range)	Mean (95% CI)	*p* Value
PASI	0	25	10.0 (3.8-42.4)	0.0 (reference)	NA
	12	23	5.8 (2.4-30.0)	5.5 (3.7-7.2)	<0.001
	24	21	4.3 (0.0-19.8)	7.7 (5.2-10.3)	<0.001
	36	15	3.6 (0.0-8.4)	7.5 (4.9-10.1)	0.001
	48	14	3.4 (0.0-11.8)	7.5 (4.6-10.5)	0.001
BSA	0	25	11.0 (3.5-72.0)	0.0 (reference)	NA
	12	23	6.0 (1.3-68.9)	6.4 (3.7-9.2)	<0.001
	24	21	2.6 (0.0-39.6)	9.8 (5.8-13.9)	<0.001
	36	15	2.3 (0.0-14.2)	10.1 (6.1-14.1)	0.001
	48	14	2.3 (0.0-9.3)	11.3 (6.9-15.6)	0.001
PGA	0	25	3.0 (2.0-5.0)	0.0 (reference)	NA
	12	23	2.1 (1.0-5.0)	0.9 (0.5-1.2)	0.001
	24	21	1.2 (0.0-5.0)	1.3 (0.8-1.9)	0.001
	36	15	1.4 (0.0-3.0)	1.4 (0.9-2.0)	0.001
	48	14	1.7 (0.0-3.0)	1.3 (0.8-1.8)	0.001
CDLQI	0	25	9.0 (2.0-20.0)	0.0 (reference)	NA
	12	23	4.6 (0.0-15.8)	5.0 (3.3-6.6)	< 0.001
	24	21	3.8 (0.0-21.0)	5.4 (3.4-7.4)	< 0.001
	36	15	3.4 (0.0-20.9)	5.4 (2.4-8.5)	0.003
	48	14	3.9 (0.0-13.3)	6.4 (2.2-10.7)	0.006

PASI, Psoriasis Area and Severity Index; BSA, body surface area; PGA, Physician Global Assessment; CDLQI, Children's Dermatology Life Quality Index; CI, confidence interval; and MTX, methotrexate. *p* Value, Wilcoxon signed-rank test, compared with baseline; NA, not applicable. Similar results were found using last observation carried forward (LOCF) analysis.

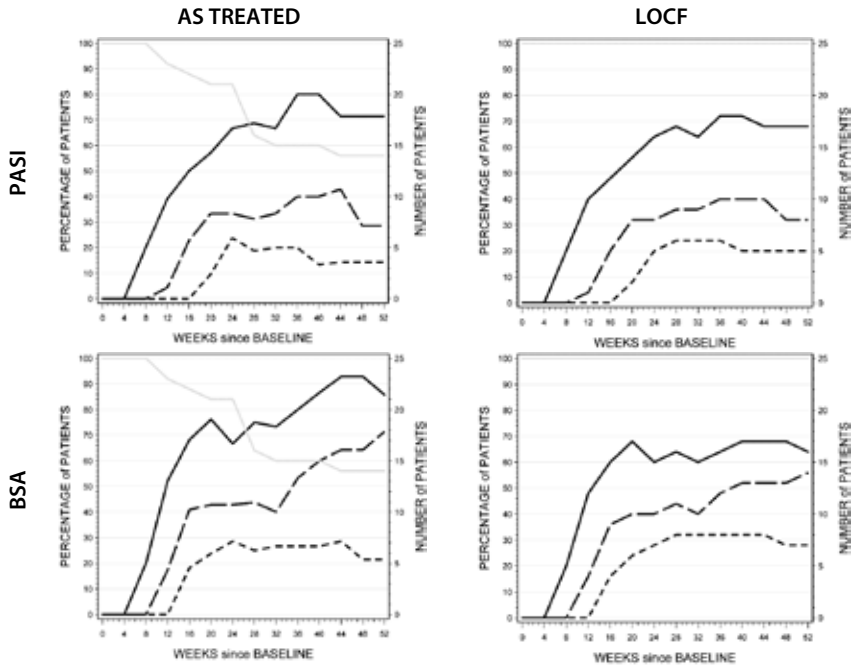

Figure 1 The percentage of improvement compared with baseline of the Psoriasis Area and Severity Index (PASI) and the body surface area (BSA), using the as treated analysis and the Last Observation Carried Forward analysis (LOCF), respectively.

The lines represent the percentage of patients with 50% improvement (black solid), the percentage with 75% improvement (long dashed), the percentage with 90% improvement (short dashed) and the number of patients (gray line).

The effectiveness of MTX related to age, BMI, WC and subcutaneous administration

We found on an average an increase in the PASI of 0.4 (95% CI: -0.3 to 1.1) per increase of one year in age at start of MTX, irrespective of the timepoint of measurement. However, this did not reach the level of statistical significance.

The PASI was not statistically significant increased neither per unit increase in BMI nor per increase in WC (0.16, 95% CI: (-0.03 to 0.35) and 0.06, 95% CI: (-0.01 to 0.13), respectively), using a linear mixed model with adjustment for baseline PASI value. So, the baseline PASI was predictive for the PASI after treatment and neither BMI nor WC was related to an additional statistical increase. Similar results were found with respect to both normal age-and sex-adjusted versus abnormal increases in WC and BMI, respectively. The mean

PASI in the age-and sex-related abnormal WC was 3.7 (95% CI: -0.5 to 7.9) and in the age-and sex-related abnormal BMI was 2.9 (95% CI: -1.4 to 7.2) higher compared to normal, irrespective of the timepoint of measurement. Again, these differences did not reach the level of statistical significance.

We found that the difference between subcutaneous and oral administration was statistically significant smaller at the later points of measurement (9.0 (95% CI: 4.1-13.8) at baseline, 6.0 (95% CI: 1.1-10.8) at 12 weeks, 4.2 (95% CI: -0.6 to 9.6) at 24 weeks and 3.6 (95% CI: -1.3, to 8.4) at 36 weeks, all in favor of oral administration). This is in line with clinical practice that 'more severe' patients have higher probability to receive subcutaneous MTX somewhere during treatment (in this study at a median time of 37.1 weeks after start MTX). The number of AEs (4/6) is not statistically significant different compared to oral MTX (11/19) (Fisher-exact, $p = 1.00$).

CDLQI

At baseline, median CDLQI was 9.0 (range 2-20); median CDLQI at week 12, 24, 36 and 48 was 4.6 (range 0-15.8), 3.8 (range 0-21), 3.4 (range 0-20.9) and 3.9 (range 0-13.3), respectively (Table 2). The median CDLQI score after 12, 24, 36 and 48 weeks was significantly lower compared with baseline.

Safety

AEs of interest were severe nausea ($n = 5$) and severe tiredness ($n = 4$). One patient experienced both nausea and tiredness. Of the eight patients with nausea and/or tiredness, three children (7-9 years old) had a maximum dose above 0.4 mg/kg/week (0.44-0.63 mg/kg), whereas the other children with nausea and/ or tiredness had a maximum dose between 0.2 and 0.3 mg/kg/week and were all adolescents. Although MTX was administrated subcutaneously in two of the eight patients because of nausea, this did not resolve the complaints.

Infections requiring antibiotics or antiviral medication were reported in five patients: one patient had a symptomatic urinary tract infection, in two patients multiple respiratory tract infections including tonsillitis occurred, one patient had a herpes zoster infection of the arm and another patient developed an eye infection (treated with topical antibiotics) and a paronychia requiring oral antibiotics. Later, he was hospitalized because of pneumonia, the only SAE reported, which resolved without sequelae. One patient reported a six-days-lasting rectal bleeding.

MTX was interrupted in two patients because of increased liver enzymes and increased creatinine, respectively. After MTX cessation, both laboratory abnormalities normalized, and MTX was subsequently reintroduced. No deaths, malignancies or bone marrow suppression were reported.

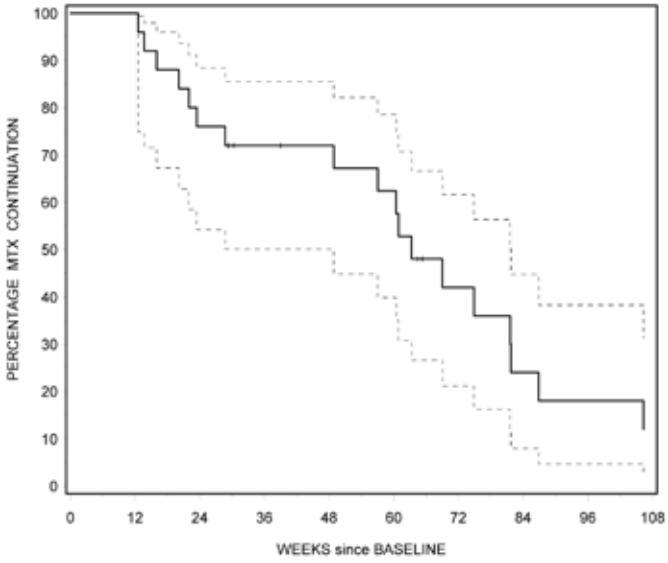

Figure 2 Kaplan-Meier estimate of the time to discontinuation of MTX.

The vertical bars indicate censored data, and the broke lines indicate the 95% confidence interval.
MTX, methotrexate.

Drug survival and reasons for discontinuation

Drug survival after 48 and 96 weeks of treatment was 72.0% (95% CI: 50.1-85.5%) and 18.0% (95% CI: 4.7-38.3%), respectively (Figure 2). Eight of 25 patients stopped using MTX ≤ 48 weeks: one patient because of severe nausea at week 12. Five patients discontinued MTX between week >12 and ≤24; one of them discontinued MTX after 22 weeks because remission was achieved and MTX became redundant. The other reasons of discontinuation were tiredness (n = 1), multiple respiratory tract infections (n = 1), a combination of nausea and ineffectiveness (n = 1) and the wish to consume alcoholic drinks (n = 1). After 28 and 48 weeks, respectively, two patients discontinued MTX because of ineffectiveness. At the time of data lock, two patients with a treatment duration of 29 and 30 weeks, respectively, were still on MTX therapy. One patient was lost to follow-up after 39 weeks of treatment and was treated elsewhere.

Fourteen of 25 patients used MTX for more than 48 weeks. Reasons for discontinuation of MTX therapy after more than 48 weeks were as follows: remission (n = 3), tiredness (n = 2), tiredness and nausea (n = 1), ineffectiveness (n = 1), combination of nausea and ineffectiveness (n = 2), pregnancy wish (n = 1) and patient's initiative (n = 1). At data lock, three of these 14 patients were still on MTX with a treatment duration of 64, 65 and 163 weeks, respectively.

Discussion

In this single center, daily clinical practice study, 25 children with psoriasis were treated with MTX of which the majority continued for more than 48 weeks. At week 24, 33.3% of patients achieved PASI 75, and the median CDLQI significantly decreased from 9.0 at baseline to 3.8. Until now, MTX treatment in pediatric plaque-type psoriasis was described in three retrospective case series with a total of 32 children.[4-6] Neither study evaluated the PGA and BSA, and only one study, including 17 patients with plaque-type psoriasis, used PASI as an objective treatment outcome measure. In this particular study, patients were treated with a once weekly oral dose of 0.2-0.4 mg/kg MTX, and an improvement in PASI of >75% was found in all but two patients. These data, however, were based on all 24 included patients, of which six patients had generalized pustular or erythrodermic psoriasis.[4] In addition, their baseline PASI was 18.4 (range 8.6-31.2), possibly at least partial because of the inclusion of children with erythrodermic and generalized pustular psoriasis. It is therefore not possible to directly compare the outcomes of this study with our results. In two randomized controlled trials (RCTs) in adults with plaque-type psoriasis, the efficacy of biologics was compared with MTX.[19,20] In the first study, 35.5% of the patients treated with MTX reached PASI 75 after 16 weeks.[19] In the other study, a PASI 75 was reached in 39.9% of patients after 24 weeks of treatment with MTX.[20] Although the results of the present study (33.3% PASI 75 after 24 weeks) are in the same range, they are somewhat disappointing. An explanation could be the low baseline PASI (median 10, and lower limit 3.8), which biases toward difficulty in achieving PASI 75. According to our daily clinical practice design, a wash-out period was not performed. Our study describes a selection of children who did not respond sufficiently to treatment with potent topical corticosteroids. Most of them (92%) did not respond to intensive day care treatment with dithranol[21] and/or phototherapy, or had a flare of their psoriasis shortly after cessation of these therapies. Within three months before starting MTX, 14 patients (56%) were treated with either systemic therapy, dithranol and/or phototherapy, which most likely explains our relatively low baseline score. Another explanation could be the daily clinical practice setting itself, of which in general is known that mostly lower response rates are found than in RCTs.[22-24]

A clinically meaningful reduction in PASI was achieved between 12 and 24 weeks of treatment (Figure 1). Several explanations are plausible for the better effectiveness of MTX at week 24: prolonged onset of clinical response, dose adjustment during follow-up or change in route of administration during follow-up. Nevertheless, we recommend continuing MTX therapy, if possible, for at least 24 weeks, before deciding that it is ineffective. This is in line with the guidelines of MTX treatment in adults.[25,26]

The median CDLQI significantly decreased from 9.0 at baseline to 3.8 at week 24. Most improvement in CDLQI occurred in the first 12 weeks of treatment, which is consistent with MTX data in adults.[27] Until now, two studies described the influence of systemic treatments on the QoL in pediatric psoriasis.[7,28] The improvement in QoL in the present

study seems to be comparable or higher than found in the other two studies,[7,28] describing an improvement in mean CDLQI with 52.3%[28] and a mean ΔCDLQI of -3.6 (95% CI: -6.4 to -0.9; $p = 0.014$[7]), respectively.

The most frequent reported AEs in our study were nausea, tiredness and respiratory tract infections. Nausea was already reported in the available literature on MTX in pediatric psoriasis[4-6], and also in other indications in children nausea is a well-known side effect.[29,30] Possibly, different treatment schedules in folic acid administration can influence the presence of nausea and other AEs; the effect of different treatment schedules of folic acid administration on the effectiveness and side effects in MTX therapy is still subject of debate[8,31] and the use and dose regimen of folic acid administration is highly variable.[32] In the pediatric psoriasis literature, tiredness was not reported until now, whereas in this study, it was reported as reason for discontinuation. Possibly, this is due to the fact that former studies[4-6] included younger patients, whereas in our study, many adolescents participated in whom tiredness was reported frequently.[33] The respiratory tract infections found in our study are difficult to interpret, as the frequency of infections in a control group of children with psoriasis is not known.

The upper limit of normal BMI varies greatly depending on the age and the sex of the child. In our study, 32% of the children had an age-and sex-adjusted BMI above the normal range. So far, it is not known whether the response to MTX in pediatric psoriasis is influenced by excess (central) adiposity or WC. We did not find a significant (additional) effect of age, (age- and sex- adjusted) BMI or WC on the effectiveness of MTX. It needs to be noted that the dosage of MTX in our study was based on the weight of the child and therefore to some extent also on BMI and WC.

In contrast, we found that subcutaneous administration of MTX has a significant higher effectiveness compared with oral MTX administration. It needs to be stressed that according to our protocol, patients were intended to be treated with MTX in a dose of 0.2-0.4 mg/kg, with a maximum starting dose of 20 mg/week. However, due to the daily clinical practice design of this study, this dose regimen was not always strictly followed due to for example overweight, AEs and patient preferences.

This study is the first to present drug survival times of MTX in the treatment of pediatric psoriasis. Our data illustrate that the majority of patients continued MTX therapy for more than 48 weeks. After 48 weeks, adherence decreased and more patients discontinued MTX therapy. This was partially due to clearance, but also because of nausea, tiredness or ineffectiveness. It would be interesting to investigate the patient characteristics of the children with long-term drug survival on MTX. For the clinician, an advise which patients should be treated with MTX would be very helpful. Based on this study, however, it is difficult to define characteristics of good responders. As we describe only a small heterogeneous cohort of pediatric patients with psoriasis, clinical interpretation is difficult, so further studies are needed in larger cohorts.

The strengths of this study are the long-term acquisition of data from a prospective daily clinical practice patient registry and the use of objective psoriasis severity and QoL scores. A limitation is the small number of patients.

Conclusion

In this small subset analysis from a longitudinal daily clinical practice cohort of pediatric plaque-type psoriasis patients, treatment with MTX shows a positive effect on PASI scores, improves QoL and has a reasonable safety profile. If possible, we recommend a treatment duration of at least 24 weeks before deciding to discontinue MTX because of ineffectiveness. A prospective, multicenter, international registry on MTX and other systemic treatments in pediatric psoriasis is highly recommended to investigate the effectiveness, QoL and safety of these treatments in this specific patient group in a consequent and standardized manner.

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2.4

Fumaric acid esters in recalcitrant pediatric psoriasis: a prospective, daily clinical practice case series

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Abstract

Background: Evidence on fumaric acid esters (FAE) in the treatment of pediatric psoriasis is scarce.

Objective: Describe the effectiveness, influence on the quality of life (QoL) and safety of FAE in children with recalcitrant psoriasis in daily clinical practice.

Methods: A prospective case series.

Results: Fourteen patients with recalcitrant plaque-type psoriasis were described (mean age 13.7, range 8-17 years). Mean treatment duration was 48.6 weeks (range 12-124). Maximum daily dose varied between 180 and 1200 mg with a mean of 564 mg per day. Mean Psoriasis Area and Severity Index (PASI) (± SEM) at baseline was 10.5 (1.0) compared to 8.6 (1.1), 6.2 (1.6) and 4.9 (1.5) at week 12, 24 and 36, respectively. An improvement in PASI was observed in nine patients (64.3%). Mean CDLQI (± SEM) at week 0, 12, 24 and 36 was 8.9 (1.4), 6.8 (1.2), 3.7 (1.4) and 3.1 (2.0), respectively. Most common adverse events (AEs) were gastrointestinal complaints (n = 13, 92.9%) and flushes (n = 10, 71.4%). Lymphocytopenia (n = 5, 45.5%) and eosinophilia (n = 4, 36.4%) were frequently observed laboratory abnormalities. AEs were usually mild and transient. One serious adverse event, unrelated to FAE, was reported.

Conclusions: FAE showed improvement of disease severity and QoL in the majority of children. Side effects occurred frequently, but were usually mild and transient. FAE may be an alternative systemic treatment option for pediatric psoriasis, provided that also the long-term safety data are closely monitored, in particular lymphocytopenia.

Introduction

Fumaric acid esters (FAE) are used in various countries and are also described in the European guideline for the treatment of psoriasis.[1] They are mostly used off label, however, in Germany a defined mix of FAE (Fumaderm®) has been licensed for moderate to severe plaque-type psoriasis in adult patients. Their mechanism of action is based on a broad range of immunomodulatory effects, in particular on the interaction of dimethylfumarate (DMF) with intra-and extracellular gluthatione.[1,2] Because of their favorable long-term safety profile, FAE are suggested to be particularly suitable for long-term treatment in adult patients with psoriasis.[3,4]

In about one-third of the patients with psoriasis, disease onset is during childhood.[5] Systemic treatments are indicated in children with moderate-to-severe psoriasis, recalcitrant to (intensive) topical treatment and/or ultraviolet B (UVB) phototherapy.[6] The management of these children can be challenging, as most systemic treatments are not approved to use in children and evidence on the efficacy and safety of systemic treatments is still sparse.[7] In this vulnerable patient group, especially long-term safety data are important. More evidence on systemic treatments is therefore highly needed, to inform physicians about the different treatment options in pediatric psoriasis.

Up to now, data on the pediatric use of FAE to treat psoriasis are scarce. The available evidence to date consists of three case reports[8-10] and two retrospective case series[11,12] with a total of 22 children. To our knowledge, prospective data are lacking. In this prospective case series, we aimed to evaluate the effectiveness, influence on the quality of life (QoL) and safety of FAE treatment in children with recalcitrant psoriasis in daily clinical practice.

Patients and methods

Data collection and study population

Data were extracted from a prospective, observational, longitudinal, long-term, daily clinical practice psoriasis registry, the Child-CAPTURE registry (Continuous Assessment of Psoriasis Treatment Use Registry).[13] The institutional review board considered this study in accordance with the applicable rules concerning the review of research ethics committee and informed consent. All children with psoriasis (age <18 years) which were treated with FAE at our outpatient clinic between September 2008 and January 2015 were analysed. Five of these patients were partially described in another publication.[11]

Treatment regimen

If possible, patients were treated according to a standardized progressive dose regimen applied in adult patients, starting with 30 mg of DMF, gradual increasing to a maximum

daily dose of 720 mg per day, based on clinical response and tolerability.[1,11] However, because this study describes a daily clinical practice, the treatment regimen could be adjusted according to the physician's opinion. Before the start of FAE, screening laboratory tests (hematological analysis, ALAT, creatinine, bilirubin) and urine analysis were performed. During the treatment, laboratory tests were conducted in accordance with the Dutch guideline for the use of FAE in adult patients.[14] Patients used additional topical treatments according to their own discretion. A wash-out period was not performed.

Outcome measures

At every visit, the Psoriasis Area and Severity Index (PASI) (score 0-72)[15] and the percentage of affected body surface area (BSA) were calculated to measure the extent and severity of psoriasis. Also, the Physician Global Assessment (PGA) was used, graded from 0-5 (0, clear; 5, very severe) to assess the overall disease severity. To quantify the impact of psoriasis on the QoL, a validated Dutch version of the Children's Dermatology Life Quality Index (CDLQI) was used.[16]

To grade adverse events (AEs) and laboratory abnormalities, the National Cancer Institute Common Toxicity Criteria (version 2.0) were used.[17] If these criteria were not applicable, AEs were judged as mild when they resolved spontaneously. AEs were defined as moderate, when there was a need for initiation of an active treatment to resolve the AE, or (temporarily) discontinuation of FAE therapy, or reduction of dosage either by the patient themselves or by the treating physician. In addition, serious adverse events (SAEs) were recorded and defined as an event that resulted in death, was life threatening, required inpatient of prolonged hospitalization, or resulted in persistent or significant disability or incapacity[18] (Table 3).

Analyses

PASI, BSA, PGA and CDLQI were interpolated to obtain outcome measures at week 12, 24 and 36. Two methods of analysis were performed: 1) as-treated analysis and 2) intention-to- treat analysis using last observation carried forward (LOCF) until 36 weeks in patients who discontinued FAE treatment. Wilcoxon signed-rank test was used to test the change since baseline of the outcomes at week 24. The statistical analyses were performed using SPSS® version 20.0 for Windows® (SPSS Inc., Chicago, IL) and Microsoft Office Excel 2007 SP3 MSO (Microsoft Corporation, Redmond, WA).

Results

Patient characteristics

The studied population consisted of 14 children (*n* = 8, 57.1% male) with recalcitrant plaque-type psoriasis treated with FAE (Table 1). The prospective data of five of these children were partially described in a primarily retrospective publication by Balak et al. for effectiveness and safety[11], but not for patient-reported outcomes. In the present study, extended data on effectiveness and safety of these patients are presented in addition to the presentation of QoL outcomes.

Mean age at the commencement of FAE therapy was 13.7 years, ranging from 8 to 17 years. All patients were previously treated with potent topical corticosteroids and most with dithranol (*n* = 12, 85.7%). In addition, 11 (78.6%) patients were (elsewhere) treated with phototherapy and/or systemic therapy at some point previous. In the 3 months prior to start of FAE, 10 of 14 patients (71.4%) were treated with systemic therapy and/or dithranol and/or phototherapy (Table 1). Two of these patients were still on dithranol treatment at the time of start FAE (6 weeks and 1 year, respectively). Concomitant topical treatments were prescribed in all patients, but one patient refused using it. Another patient started with dithranol therapy 7 weeks after the initiation of FAE because of insufficient clinical response.

FAE formulation and dosage regimen

In all patients, DMF was prescribed by the physician. According to the Dutch regulations, the original manufacturer is up to the pharmacist. Due to this system, 8 of 14 patients (57.1%) were treated with a Dutch FAE formulation with *slow-release* tablets of DMF. Another Dutch formulation of *non-slow-release* tablets of DMF was given to six patients (Table 1).

The maximum daily dose varied between 180 and 1200 mg with a mean of 564 mg per day. Most patients (*n* = 8; 57.1%) were treated according to a standardized progressive dose regimen applied in adult patients with a maximum daily dose of 720 mg per day, based on clinical response and tolerability.[1,11] In four patients, a more gradual increase in dosages was applied, resulting in lower maximum dosages (180, 270, 240 and 360 mg, respectively). Two patients exceeded the maximum daily dose of 720 mg per day. In one patient, the maximum daily dose was increased up to 960 mg because of insufficient response at 720 mg. The other patient was treated elsewhere because of the distance, up to a maximum dose of 1200 mg daily.

Treatment duration and reasons for discontinuation

The mean treatment duration was 48.6 weeks with a range of 12-124 weeks (Table 1). At the time of data lock, five patients were still on FAE treatment. As two patients were referred to another hospital, it is unknown whether these patients are still on treatment.

Table 1 Patient characteristics.

ID	Sex	Type of psoriasis	Age at onset (y)	Previous therapy	Therapy <3 mo before FAE	Age at start of FAE (y)	FAE formulation
1	M	Plaque	2	Potent cs, dithranol 3x, UVB, MTX, Etanercept	UVB, topical	12	DMF sr
2	F	Plaque	12	Potent cs, dithranol, UVB, MTX	Topical	17	DMF sr
3	M	Plaque	9	Potent cs, dithranol, UVB	Topical	14	DMF
4	M	Plaque	7	Potent cs, dithranol 2x, UVB	Dithranol, topical	10	DMF sr
5	F	Plaque	6	Potent cs, UVB 3x, MTX, cyclosporine	MTX, topical	17	DMF sr
6	M	Plaque	2	Potent cs, dithranol, UVB 2x	Dithranol, topical	8	DMF
7	M	Plaque	14	Potent cs, dithranol, MTX	MTX	16	DMF
8	F	Plaque	7	Potent cs, dithranol 4x, UVB 3x	Topical	17	DMF
9	F	Plaque	12	Potent cs, UVB	UVB	13	DMF sr
10	M	Plaque	9	Potent cs, dithranol 3x	Dithranol, topical	14	DMF
11	M	Plaque	8	Potent cs, dithranol 2x	Dithranol, topical	11	DMF sr
12	F	Plaque	13	Potent cs, dithranol, UVB	Dithranol, topical	17	DMF sr
13	F	Plaque	6	Potent cs, dithranol, PUVA	Topical	17	DMF
14	M	Plaque	8	Potent cs, dithranol	Dithranol, topical	9	DMF sr

M, male; F, female; cs, corticosteroids; UVB, ultraviolet B phototherapy; MTX, methotrexate; PUVA, Psoralen plus ultraviolet A phototherapy; NA, not applicable; FAE, fumaric acid esters; DMF, dimethylfumarate; sr; slow-release; mo, months; y, years; wk, weeks; mg, milligram; kg/m^2, kilogram per square meter; cm, centimeter.

[a] Already treated with dithranol for 6 weeks.

[b] Already treated with dithranol for almost 1 year.

[c] Started additional dithranol treatment after 7 weeks of FAE therapy because of insufficient clinical response.

The other seven patients discontinued FAE therapy: two patients because of ineffectiveness, two because of AEs and two patients because of a combination of ineffectiveness and AEs. One patient had to stop FAE because of psoriatic arthritis that needed methotrexate treatment. The AEs resulting in discontinuation of FAE were persistent lymphocytopenia (about 1 year) and a persistent cough. A combination of ineffectiveness and AEs (flushes

Maximum daily dose (mg)	Maintenance daily dose (mg)	Treatment duration (weeks)	Reasons for discontinuation	Concomitant therapy	BMI (kg/m^2)	Waist circumference (cm)	Family history psoriasis
960	960	47	NA	Topical	20.2	72	No
720	720	110	NA	Topical	25.8	89	No
720	720	49	NA	Topical	20.1	73	Yes
180	-	21	Arthritis	Dithranol[a], topical	17.4	67	Yes
270	-	48	Unknown	Topical	25.5	93	Yes
240	-	35	Ineffectiveness	Dithranol[b], topical	14.8	56	Yes
720	-	12	Ineffectiveness	None	36.8	132	Yes
360	-	15	Ineffectiveness + adverse events	Topical	23.3	65	Yes
1200	-	124	Unknown	Topical	15.9	62	No
480	-	16	Ineffectiveness + adverse events	Dithranol[c], topical	18.2	70	No
480	360-480	51	NA	Topical	16.4	57	No
600	-	68	Adverse events	Topical	24.0	86	Yes
480	-	32	Adverse events	Topical	18.5	70	Yes
480	240-480	52	NA	Topical	15.8	62	No

and tiredness versus transient lymphocytopenia) were the other reasons. Patient 12 discontinued FAE treatment after 5 weeks because of a severe episode of flushes after the first intake of a tablet of 120 mg FAE, which resolved with oral prednisone and oral histamine antagonists. After more than 4 months, FAE was reintroduced and continued for 63 weeks.

Effectiveness

Disease severity: as treated analysis

At baseline and at week 12, 24 and 36 PASI, BSA and PGA were available in 14, 14, 8 and 7 patients, respectively (Table 2a). Mean PASI ± SEM at baseline was 10.5 (1.0) compared with 8.6 (1.1), 6.2 (1.6) and 4.9 (1.5) at week 12, 24 and 36, respectively. At week 24, mean PASI had statistically significantly improved compared to baseline ($p = 0.025$). Mean BSA and PGA ± SEM at baseline and at week 12, 24 and 36 and the percentage of improvement are described in Table 2(a). An overall reduction in PASI was observed in 9 of 14 patients (64.3%), while in one patient the psoriasis severity hardly changed. PASI worsened in the other four patients. It is remarkable that all patients which were treated with the *slow-release* tablets of DMF ($n = 8$) showed an improvement in PASI score.

Table 2 PASI, BSA, PGA and total CDLQI of the children with plaque-type psoriasis treated with FAE at several time points.

Outcome	Weeks since baseline	No. of patients	Observed mean (SEM)	Change since baseline mean (95% CI)
(a) As treated analysis				
PASI	0	14	10.5 (1.0)	0.0 (reference)
	12	14	8.6 (1.1)	1.9 (-0.3 to 4.2)
	24	8	6.2 (1.6)	5.5 (1.7 to 9.2)
	36	7	4.9 (1.5)	7.0 (3.4 to 10.5)
BSA	0	14	13.8 (2.3)	0.0 (reference)
	12	14	12.6 (2.3)	1.2 (-3.7 to 6.1)
	24	8	8.1 (2.9)	9.0 (0.7 to 17.3)
	36	7	5.5 (2.9)	12.1 (2.9 to 21.3)
PGA	0	14	3.4 (0.2)	0.0 (reference)
	12	14	3.0 (0.2)	0.4 (-0.1 to 0.8)
	24	8	2.2 (0.4)	1.3 (0.3 to 2.3)
	36	7	2.0 (0.5)	1.6 (0.6 to 2.6)
CDLQI	0	11	8.9 (1.4)	0.0 (reference)
	12	11	6.8 (1.2)	2.1 (-0.2 to 4.3)
	24	6	3.7 (1.4)	3.0 (-0.1 to 6.1)
	36	5	3.1 (2.0)	4.1 (0.5 to 7.7)

Table 2 Continued.

Outcome	Weeks since baseline	No. of patients	Observed mean (SEM)	Change since baseline mean (95% CI)
(b) Last Observation Carried Forward analysis				
PASI	0	14	10.5 (1.0)	0.0 (reference)
	12	14	8.6 (1.1)	1.9 (-0.3 to 4.2)
	24	14	7.5 (1.4)	3.0 (0.1 to 6.0)
	36	14	7.3 (1.4)	3.2 (0.1 to 6.4)
BSA	0	14	13.8 (2.3)	0.0 (reference)
	12	14	12.6 (2.3)	1.2 (-3.7 to 6.1)
	24	14	10.2 (2.5)	3.7 (-2.9 to 10.2)
	36	14	9.5 (2.5)	4.3 (-2.7 to 11.3)
PGA	0	14	3.4 (0.2)	0.0 (reference)
	12	14	3.0 (0.2)	0.4 (-0.1 to 0.8)
	24	14	2.6 (0.3)	0.8 (0.1 to 1.5)
	36	14	2.5 (0.4)	0.9 (0.1 to 1.6)
CDLQI	0	11	8.9 (1.4)	0.0 (reference)
	12	11	6.8 (1.2)	2.1 (-0.2 to 4.3)
	24	11	5.2 (1.2)	3.7 (1.1 to 6.4)
	36	11	5.1 (1.3)	3.9 (1.1 to 6.6)

PASI, Psoriasis Area and Severity Index; BSA, Body Surface Area; PGA, Physician Global Assessment; CDLQI, Children's Dermatology Life Quality Index; CI, confidence interval; FAE, fumaric acid esters; LOCF, Last Observation Carried Forward.

Disease severity: LOCF analysis

Mean PASI ± SEM at baseline was 10.5 (1.0) compared with 8.6 (1.1), 7.5 (1.4) and 7.3 (1.4) at week 12, 24 and 36, respectively. At week 24, PASI improved compared to baseline (p =0.056). Mean BSA and PGA ± SEM at baseline and at week 12, 24 and 36 and the percentage of improvement are described in Table 2(b).

Quality of life

At baseline, CDLQI was available in 11 patients, with a mean ± SEM of 8.9 (± 1.4). At week 12, 24 and 36 CDLQI were available in 11, 6 and 5 patients, respectively. Mean CDLQI ± SEM

Table 3 Adverse events.

Characteristic	*N* = 14 (%)	Mild, *n* (%)	Moderate, *n* (%)	Severe, *n* (%)
Adverse events	14/14 (100)			
Gastrointestinal complaints	13 (92.9)			
• Diarrhea	10 (71.4)	6 (42.9)	4 (28.6)	-
• Abdominal pain	8 (57.1)	5 (35.7)	3 (21.4)	-
• Abdominal cramps	3 (21.4)	3 (21.4)	-	-
• Nausea	3 (21.4)	3 (21.4)	-	-
• Vomiting	2 (14.3)	1 (7.1)	1 (7.1)	-
• Reflux	1 (7.1)	1 (7.1)	-	-
• Flatulence	1 (7.1)	1 (7.1)	-	-
• Stomache ache	1 (7.1)	-	1 (7.1)	-
Flushing, burning sensation and/or reddening of the skin	10 (71.4)	6 (42.9)	4 (28.6)	-
Infections	6 (42.9)			
Episodes[a]				
• Respiratory tract	4	1	3	-
• Skin	3	-	3	-
• Gastrointestinal tract	2	1	1	-
Headache	4 (28.6)	3 (21.4)	1 (7.1)	
Tiredness	3 (21.4)	1 (7.1)	2 (14.3)	-
Musculoskeletal complaints[b]	3 (21.4)	2 (14.3)	-	1 (7.1)
Other[c]	1 (7.1)	1 (7.1)	-	-

Laboratory adverse events	9/11 (81.8%)			
Lymphocytopenia	5 (45.5) Reference (1.5-3.5 x $10^9 l^{-1}$)	1.0 to < 1.5	0.5 to <1.0	< 0.5
		3 (27.3)	1 (9.1)	1 (9.1)
Eosinophilia	4 (36.4) Reference (< 0.5 x $10^9 l^{-1}$)	0.5 to < 1.0	1.0 to < 1.5	≥ 1.5
		2 (18.2)	-	2 (18.2)
Monocytosis	1 (9.1) Reference (0.2-0.8 x $10^9 l^{-1}$)	1 (9.1) Maximum 1.05 x $10^9 l^{-1}$	-	-
Creatinine				
• Below normal range	2 (18.2) Reference (45-95 umol/l)	2 (18.2) (38 and 41 umol/l resp.)	- - -	- -
• Normal range	9 (81.8)	-		-
• Above normal range	-	-		
Liver enzymes				
• Increase in ALAT	3 (27.3) Reference (<35 U/l)	3 (27.3) (63, 39 and 62 U/l resp.)	-	-

Data are number of patients (percentages).

[a] One patient had one episode of fever, vomiting, and nausea (1 week). Another patient had a sinusitis (treated with antibiotics), an episode of flu/common cold and a mycosis of the groins and interdigital feet treated by topical antimycotics. A third patient was treated because of scabies. A fourth patient had one episode of gastroenteritis treated with omeprazol 20 mg once daily for 5 days. A fifth patient developed pityriasis versicolor treated by topical antimycotics. The sixth patient developed an ear infection and was treated because of a persistent cough.

[b] Pain in legs during exercise; painful sensation on the medial side of the right ankle; fracture of the left clavicula after trauma.

[c] Cold hands.

at week 12, 24 and 36 was 6.8 (1.2), 3.7 (1.4) and 3.1 (2.0), respectively. Using LOCF, mean CDLQI ± SEM at week 12, 24 and 36 was 6.8 (1.2), 5.2 (1.2) and 5.1 (1.3), respectively (Table 2). At week 24, CDLQI significantly improved compared to baseline in both the as treated analysis (p =0.046) and LOCF analysis (p =0.016).

Safety

AEs were reported by all patients (Table 3). The most common AEs were gastrointestinal complaints (n = 13, 92.9%) and flushes (n = 10, 71.4%). Most frequently reported gastrointestinal complaints were diarrhea (n = 10, 71.4%) and abdominal pain (n = 8, 57.1%) which were usually mild and transient. In four patients, the gastrointestinal complaints were judged as moderate, because either a brief additional treatment was given for their diarrhea (antidiarrheal), or FAE was temporary decreased. In all four patients, the complaints did not result in a discontinuation of FAE. In six patients (42.9%), a total of nine infections were reported including four respiratory tract infections, three skin infections and two gastrointestinal tract infections. All these infections were mild or moderate and were self-limiting or treated with oral and/or topical therapy. One patient developed a fracture of the left clavicle after trauma which was unrelated to the studied medication and was the only SAE in this cohort.

Routine laboratory tests were available in 11 patients. In three patients laboratory tests were performed elsewhere in other hospitals. Abnormal laboratory tests were observed in 9 of 11 patients (81.8%). Most common laboratory abnormalities were lymphocytopenia (n = 5, 45.5%) and eosinophilia (n = 4, 36.4%). Lymphocytopenia was observed in five patients. In three of these patients, the lymphocytopenia was mild and transient. Another patient treated with 480 mg DMF per day developed once a severe lympocytopenia (0.45 x 10^9 l^{-1}; reference 1.5-3.5 x 10^9 l^{-1}). This lymphocytopenia was transient and fully reversible after temporarily reducing the dose by 50%. In another patient, a long-lasting moderate lymphocytopenia (minimum value 0.65 x 10^9 l^{-1}) was the reason to discontinue the FAE treatment. This is the only patient with lymphocytopenia who developed an infection (pityriasis versicolor).

Eosinophilia was observed in four patients. Two patients had a mild eosinophilia (0.5-1.0 x 10^9 l^{-1}), and two a severe eosinophilia (≥1.5 x 10^9 l^{-1}), with a maximum level of 3.82 x 10^9 l^{-1} in one patient. The mild eosinophilia was already present before start of FAE therapy in one patient. In all patients, the eosinophilia was transient and fully reversible. A mild monocytosis was found in one patient which completely resolved. While a slight decrease in creatinine was found in two patients, an increase in creatinine was not observed. Finally, a slight increase in ALAT was observed in three patients; this increase was less than twice the upper limit of normal in all patients.

Discussion

In this prospective, daily clinical practice case series, 14 children with recalcitrant plaque-type psoriasis were treated with FAE. In the majority of these children, FAE treatment showed an improvement in PASI and QoL. Although AEs occurred frequently, they were usually mild and transient.

This case series is unique as it describes the efficacy and safety of FAE in pediatric psoriasis patients with a high historical severity, as most were treated with intensive topical treatment, dithranol[19], phototherapy and/or systemics. In addition, the influence of FAE therapy on the QoL was reported, which was never investigated before.

In our study, mean PASI significantly improved from 10.5 at baseline to 6.2 at week 24. This response seemed to be lower than found in previous case series in which the efficacy of FAE in pediatric psoriasis was described. Until now, in addition to three case reports[8-10], there are two retrospective case series[11,12], in which a total of 22 children were described. In the largest of these case series, complete clearance was found in 36% of patients, good improvement in 7%, partial response in 21% and non-response in 36%.[11] However, PASI was only available in six patients.[11] Another case series described six children treated with Fumaderm®. All patients (three of which had guttata psoriasis) achieved an improvement in PASI of at least 75% or more. However, in four of these patients, an additional tonsillectomy was performed.[12] In the three pediatric case reports, FAE treatment resulted in impressive decreases of PASI scores.[8-10]

An explanation for the lower response rates found in our study could be the selection of plaque-type psoriasis patients with a high historical severity recalcitrant to topical therapy (n = 14), dithranol (n = 12), phototherapy and/or systemics (n = 11). In addition, a washout period before commencement of FAE was not performed, resulting in a relatively low baseline PASI (10.5).

Another explanation for the differences in response rates might be the use of dissimilar FAE formulations or release forms in several studies. Whereas Fumaderm® (a commercial mixture of DMF and three salts of ethyl hydrogen fumarate)[1] was used in all German cases[8,9,12], all patients in our study were treated with monotherapy DMF. Eight patients were treated with the *slow-release* form, whereas six patients were treated with the *non-slow-release* form. Remarkably, of the nine patients with an improvement in PASI, eight were treated with the *slow-release* form. In such small patient populations, it remains an open question whether formulation and release forms influence the effectiveness and side effects of FAE. Therefore, prospective comparative studies are needed to investigate this issue.

As psoriasis can have a negative impact on the QoL in children, that can be improved by treatment[20,21], it is important to assess patient-reported outcomes. In our patients the CDLQI improved from 8.9 at baseline to 3.7 at week 24 (58.4%). To our knowledge, data on the influence of FAE treatment on the QoL in pediatric psoriasis are lacking. However,

methotrexate treatment in pediatric psoriasis resulted in an improvement in CDLQI from 9.0 at baseline to 3.8 at week 24 (57.8%)[13], whereas etanercept treatment resulted in 52.3% improvement in CDLQI from baseline to week 12.[22] Therefore, the influence of FAE on the QoL of children with psoriasis seems to be in accordance with the available literature on other systemic treatments.

Although AEs occurred frequently in our 14 patients, they were usually mild and transient (Table 3). The most common AEs were gastrointestinal complaints (*n* = 13, 92.9%) and flushes (*n* = 10, 71.4%). Lymphocytopenia (*n* = 5, 45.5%) and eosinophilia (*n* = 4, 36.4%) were frequently observed laboratory abnormalities. The frequency and type of the AEs found in our study are in accordance with those found in both children[11,12] and adults.[1,3,23-26] In the adult literature, two long-term safety considerations were found that need special attention in children. First, several case reports of acute renal failure or Fanconi syndrome were described.[27-32] In our study, a slight decrease in creatinine was found in two patients, whereas an increase in creatinine was not observed. The other safety consideration regards long-term lymphocytopenia. In 2003 long-term safety data up to 14 years on FAE therapy in adult psoriasis patients were reported.[3] Although the development of malignancies or an increased risk of infections was not observed[1,3], a relative lymphocytopenia of <20% occurred frequently in 76% of the patients.[3] Lymphocytopenia is a well-known side effect of FAE[1] and it is hypothesized that long-term immunodeficiency may be related to the development of progressive multifocal leukoencephalopathy (PML).[33,34] Recently, some cases of PML after treatment with FAE were described in adult psoriasis patients.[33,35-39] Because of the described association in the literature between long-term lymphocytopenia and PML, it is of utmost importance to avoid long-term lymphocytopenia in children treated with FAE. Therefore, we decided to discontinue FAE treatment in the one patient who had a long-lasting moderate lymphocytopenia (minimum value 0.65 x 10^9 l^{-1}).

The strengths of the present study are the extraction of data from a prospective, daily clinical practice registry and the use of objective outcome measures to assess disease severity and the impact on QoL. Although this study is limited by the small number of patients, it represents the largest prospective series of children with recalcitrant psoriasis treated with DMF so far.

Conclusion

In this prospective daily clinical practice cases series of 14 children with plaque-type psoriasis, FAE lead to improvement of disease severity and QoL in the majority of patients. Although AEs occurred frequently, mostly gastrointestinal complaints and flushes, they were usually mild and transient. As there is still limited evidence on the efficacy and safety of FAE treatment in pediatric psoriasis, and in particular a lack on long-term safety, the position of FAE in the systemic treatment of pediatric psoriasis is not clear. Nevertheless,

FAE may be an alternative systemic treatment option to manage pediatric psoriasis, provided that also the long-term safety data are closely monitored, in particular lymphocytopenia.

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2.5

An outpatient multidisciplinary training programme for children and adolescents with psoriasis and their parents: a pilot study

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Pediatric psoriasis can have a profound impact on the lives of patients.[1] For adult psoriasis patients, multidisciplinary training programmes, as an adjunct to standard dermatological treatment, can improve physical and psychosocial wellbeing.[2,3] However, studies on training programmes for pediatric psoriasis are scarce.[4]

This pilot study aimed to assess patient and parent satisfaction with a previously described outpatient multidisciplinary training programme for children and adolescents with psoriasis and their parents.[5] In addition, patients' and parents' perceived improvement in coping, their complaints, as well as their evaluation on the importance of specific training modules, were studied. Finally, the influence of this programme on quality of life (QoL), itch and scratch responses, illness cognitions, and impact on family life were assessed.

The training comprised four sessions of 2.5 hours over a 10-week period. The programme was designed for two age-related groups (6-12 and 12-18 years) and included several modules: (1) medical information and daily skin care; (2) itch and scratch problems, and coping with the pain; (3) coping, self-esteem, sleep hygiene and relaxation exercises; and (4) preventing relapse.[5,6]

At the end of the training, an evaluation questionnaire was completed by patients and parents to assess satisfaction (scale: 1-10), overall usefulness (scale: 1-10), usefulness of specific aspects of the programme (scale: 0-6), improvement in coping and complaints (4-point Likert scale; 1=no improvement; 2=little improvement; 3=much improvement; 4=very much improvement), and importance of the training modules (4-point Likert scale; 1=not important; 2=little important; 3=fairly important; 4=very important). Additionally, before and after the training and after three months of follow-up, the Children's Dermatology Life Quality Index (CDLQI)[7], Impact of Chronic Skin Disease on Daily Life (ISDL)[8], Stein Impact on Family Scale (SIFS)[9], and Dermatitis Family Impact (DFI)[10] were completed by patients and/or parents. These self-reported questionnaires were also completed at corresponding measurement points (zero, three and six months) by an age and gender-matched control group of pediatric psoriasis patients.

Twenty-three of 25 participants (65% female) completed the programme. Median age was 11.0 years (range: 6-17). Sixty-five per cent of the patients participated in the younger group (6-12 years). The sex and median age of the control group (n = 23) were identical. Psoriasis Area and Severity Index (PASI) was slightly higher in the control group compared to participants (4.5 versus 3.3), but this was not statistically significant (Mann-Whitney test; p = 0.20). In both groups, the majority was treated with topicals. Descriptive analysis of the data indicated that patients and parents were highly satisfied with the programme (median; patients: 8.0; parents: 9.0). Parents rated the overall usefulness high (8.0). In addition, the group format (6.0) and multidisciplinary character (5.5) were indicated as very useful. All parents would recommend the programme to others.

Between 48% and 100% of patients and parents reported subjective improvement in coping, in particular with regard to daily skin care, itching and scratching, and social encounters. Indeed, >90% of patients had less complaints about itching and scratching and a better mood. Most patients and parents considered all modules to be important. Regarding age group differences, younger children were more satisfied (10.0) than adolescents (7.5). Also, the parents of children were more satisfied (10.0) than the parents of adolescents (8.0).

The self-reported questionnaires (CDLQI, ISDL, SIFS and DFI) showed positive changes in outcomes for participants, including improvements in QoL, itching, scratching, helplessness, acceptance, and impact on family life (Table 1). However, these improvements were also found in the control group. The severity of psoriasis (measured by the PASI) hardly changed for participants and controls. An explanation for these results could be the selection of patients. This training might be more relevant to patients who are at risk of psychological adjustment problems. Furthermore, most questionnaires were not validated for use in children, and self-assessment questionnaires may have been affected by several biases, *e.g.* social desirability or response bias. In addition, the control group consisted of children who refused participation in the programme which could have biased the outcomes.

In conclusion, this pilot study indicated that an outpatient multidisciplinary training programme for children and adolescents with psoriasis and their parents was well-accepted and positively evaluated. The majority of patients reported subjective improvements in coping and physical and psychosocial wellbeing.

Table 1 The outcomes on the self-reported questionnaires and disease severity.

		Baseline		End of programme		Three-month follow-up	
Questionnaires		**Median (range)**	**No**	**Median (range)**	**No**	**Median (range)**	**No**
Quality of life							
CDLQI[1]	P	5.0 (0.0-14.0)	23	4.0 (0.0-18.0)	23	3.0 (0.0-14.0)	21
	C	2.0 (0.0-10.0)	21	2.0 (0.0-7.0)	21	1.0 (0.0-5.0)	19
Itch and scratching							
ISDL-itch total[1]	P	5.9 (3.0-12.4)	23	5.6 (3.0-10.6)	23	4.4 (3.0-12.8)	21
	C	4.2 (3.0-9.5)	21	4.6 (3.0-11.6)	21	3.1 (3.0-10.3)	19
ISDL-scratch total[1]	P	11.0 (7.0-20.0)	23	12.0 (7.0-16.0)	23	9.0 (7.0-20.0)	21
	C	10.0 (7.0-20.0)	21	10.0 (7.0-20.0)	21	9.0 (7.0-17.0)	19
Illness cognitions							
Helplessness (ISDL)[1]	P	7.0 (6.0-12.0)	23	6.0 (6.0-16.0)	23	6.0 (6.0-12.0)	21
	C	7.0 (6.0-11.0)	21	6.0 (6.0-11.0)	21	6.0 (6.0-11.0)	19
Acceptance (ISDL)[1]	P	18.0 (8.0-24.0)	23	17.0 (10.0-24.0)	23	21.0 (11.0-24.0)	21
	C	21.0 (11.0-24.0)	21	20.0 (17.0-24.0)	21	20.0 (13.0-24.0)	19
Family impact							
DFI[2]	P	3.0 (0.0-19.0)	23	3.0 (0.0-15.0)	21	1.5 (0.0-12.0)	20
	C	2.0 (0.0-17.0)	21	1.0 (0.0-9.0)	21	0.0 (0.0-7.0)	18
SIFS[2]	P	58.0 (41.0-60.0)	22	58.0 (47.0-60.0)	18	59.5 (51.0-60.0)	20
	C	60.0 (39.0-60.0)	21	60.0 (50.0-60.0)	21	60.0 (50.0-60.0)	17
Disease severity							
PASI	P	3.3 (0.0-11.5)	23	4.1 (0.6-8.4)	22	3.7 (0.0-9.9)	18
	C	4.5 (0.6-12.0)	11	4.8 (0.4-18.8)	10	4.0 (0.0-16.8)	9

[1] Patient-reported; [2] Parent-reported; CDLQI: Children's Dermatology Life Quality Index; ISDL: Impact of Chronic Skin Disease on Daily Life; SIFS: Stein Impact on Family Scale; DFI: Dermatitis Family Impact; PASI: Psoriasis Area and Severity Index; P: Participants; C: Controls.

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Chapter 3

Assessment measures on disease severity and psychosocial impact

3.1

A pilot study on the Psoriasis Area and Severity Index (PASI) for small areas: presentation and implications of the Low PASI score

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Abstract

Background: The Psoriasis Area and Severity Index (PASI) is not able to measure small affected areas in a body region which is important for assessing the performance of high-effective treatment.

Objective: To present the Low PASI score, show the difference between the classic PASI and the Low PASI, evaluate the interobserver agreement of both scores, and compare the two scores within investigators.

Methods: Cross-sectional study. Two investigators independently assessed the classic PASI and the Low PASI in 10 patients with mild-to-moderate plaque psoriasis. Differences in outcome between the two scores were calculated. Intraclass correlation coefficients (ICC) were used to determine the interobserver agreement and to compare measurements of the two scores within both investigators. Prediction limits of 95% for the errors in measurements were provided.

Results: In both investigators, Low PASI was mean 1.71 and 1.76, whereas the classic PASI was mean 4.14 and 4.33. The interobserver agreement (ICC) was excellent for both investigators in both scores (ICC classic PASI = 0.95 and Low PASI = 0.87).

Conclusion: The Low PASI score allows more possible scores at lower levels of psoriasis extent (affected areas lower than 10% in a body region) compared to the classic PASI. This new score may lead to a more precise analysis of treatment responses and may have important clinical implications.

Introduction

In patients with psoriasis, it is important to measure the severity of the disease in order to monitor changes induced by treatment in both clinical trials as well as in daily clinical practice.

The most widely used tool to assess disease severity and extent is the Psoriasis Area and Severity Index (PASI).[1-3] The PASI score is usually calculated before, during and after treatment, and allows us to determine how well patients with psoriasis respond to that treatment. Nowadays, for clinical decision making, both the change in absolute PASI is used, as well as the percentage of PASI improvement such as PASI 50. PASI 50 denotes a reduction of 50% of the PASI score of a single patient, compared to the PASI score at the start of the intervention. Since the introduction of very effective treatments such as the biologics, many patients reach PASI 75 or PASI 90 after treatment. At this point, the most important and widely criticized limitation of the classic PASI score arises, namely that this PASI score is insufficient to measure and discriminate involved areas lower than 10% of a body region. A minimal involvement (lower than 10% of the body area involved) will always lead, according to the classic PASI six-point area scale classification, to an area of 1.[1,4-8] Consequently, reduction of areas of minimal involvement will not lead to changes in the outcome of the classic PASI score. However, a change in the severity scores (erythema, induration and desquamation) of the lesions might change the outcome of the classic PASI score. This means that the classic PASI score in the smallest involved areas does not give an accurate representation of the involvement of the affected skin and of the real clinical improvement.[8] For this purpose, a PASI for small affected areas is needed. Therefore, we developed the Low PASI score, a refined PASI score for psoriasis patients with small involved areas.

For example, a patient with one psoriasis plaque of 8 cm (lower than 10% of the body area involved) on each body region, with minimal erythema, induration and desquamation, will have a classic PASI score of 3. If the plaque improves 4 cm (in each body region), without any change on erythema, induration and desquamation, the absolute score will remain 3. Although, there is a clinically perceptible improvement, this will not be reflected in the classic PASI score. This implies that the reduction of the PASI score could easier be reached in a larger percentage of patients than the present classic PASI score indicates.

In order to assess the effectiveness of treatments more accurately, it is important to enable a good assessment of the small involved areas (affected areas lower than 10% of each body region).

The aim of this study is to present the Low PASI score (a PASI score refined for patients with small involved areas) and to show the difference between the absolute PASI scores achieved with the classic PASI and the Low PASI. In addition, to evaluate the interobserver agreement of the classic PASI and the Low PASI and to compare the measurements of the two scores within both investigators.

Methods

Participants

In the period between 1st October 2013 and 6th March 2014, 10 psoriasis patients visiting the outpatient clinic of the department of Dermatology at the Radboud University Medical Center were enrolled. Inclusion criteria were: age of at least 18 years, mild-to-moderate plaque psoriasis, and involvement of at least one body area involvement lower than 10%.

Study design

In this cross-sectional study, two investigators (experienced PASI assessors), independently assessed the classic PASI score and the Low PASI score of the included patients at the same day. This study did not required approval from an institutional review board according to ethics guidelines in the Netherlands.

Psoriasis Area and Severity Index (PASI)

The classic Psoriasis Area and Severity Index (PASI) score assesses the extent and severity of psoriasis. The extent of psoriasis is measured by the body area involved and the severity by erythema (E), induration (I) and desquamation (D) of the plaques.

The body area involved is the percentage of area involved in a particular body region. For calculating classic PASI, the body is divided into four body regions: head (H), upper extremities (U), trunk (T), and lower extremities (L). These four body regions correspond to approximately 10, 20, 30, and 40% of the total body surface area (BSA), respectively. One per cent of the BSA is for the purpose of clinical estimation equivalent approximately to the total palmar surface (palm plus five digits) or a 'handprint' of the patient.[9] Converting a handprint (1% BSA) to the extent of each body region (H = 10%, U = 20%, T = 30% and L = 40%) results in approximately: 1/10 = 10% of the head, 1/20 = 5% of the upper extremities, 1/30 = 3.3% of the trunk, and 1/40 = 2.5% of the lower extremities.

The body area involved in a body region is classified into a six-point scale called area (A): 1, < 10% involvement; 2, 10 - 29%; 3, 30 - 49%; 4, 50 - 69%; 5, 70 - 89%; 6, 90 - 100%.

The severity of psoriasis in a body region is the sum of the scores for erythema, induration and desquamation in that body region, and each is assessed according to a four-point scale: 0, no symptoms; 1, slight symptoms; 2, moderate symptoms; 3, marked symptoms; 4, very marked symptoms.

Calculating classic PASI, the classified body area involved (A), and the severity parameters are assessed for each of the four body regions (H, U, T and L), separately. Subsequently, A and the disease severity [erythema (E), induration (I) and desquamation (D)] are multiplied, and the result of this is multiplied by the BSA that corresponds to the assessed body region; 0.1 (H); 0.2 (U); 0.3 (T) or 0.4 (L). The sum of the PASI scores for all four body regions is the total classic PASI score.

The total classic PASI score is calculated using the following formula:

PASI = 0.1 x (EH+ IH+ DH)AH+ 0.2 x (EU+ IU+ DU)AU + 0.3 x (ET+ IT+ DT)AT+ 0.4 x (EL+ IL+ DL)AL[1]

The total classic PASI score ranges from 0 to 72.[1]

Low Psoriasis Area and Severity Index (Low PASI)

Low PASI comprises the same components as the classic PASI. To refine the body areas involved lower than 10%, we divided the area score of the classic PASI into four fractional components that are reflected in a four- point scale also called area (A): 0.25, 0.1 - 2.5% involvement; 0.50, 2.6 - 5%; 0.75, 5.1 - 7.5%; 1, 7.6 - 9.9%.

This means that an involved area of a half 'handprint' (0.5% of the BSA) on the head (10%), converted to that body area, as we earlier explained, will result in 0.5/0.1= 5% of the head involved, this is equivalent of a classified body area involved of A equal to 0.5. In the classical PASI, this would be an A equal to 1 (Table 1).

Statistical methods

Linear mixed models were used to study the interobserver agreement of the PASI and the Low PASI, separately. Note that a linear mixed model is an extension of a linear regression model. The dependent variable was the PASI score (Low PASI, respectively). The independent class variable was investigator (two levels), and the intercept of each patient was treated as a random variable. The intraclass correlation coefficient (ICC) of agreement with the 95% confidence interval (CI) and the mean difference between the investigators with 95% CI are presented.

Similar linear mixed models were used to study differences between the two methods of each investigator, separately. At this point, the independent class variable was method (two levels: PASI, Low PASI). Again, the ICC (95% CI) and the mean difference (95% CI) are presented. The ICC assesses the consistency, or conformity, of measurements made by the two investigators (the two methods, respectively) measuring the same event simultaneously and independently.[10] Values of the ICC range from 0 to 1, with a higher value indicating better reliability. ICC less than 0.40 is considered as poor; 0.40 to 0.59 as fair; 0.60 to 0.74 as good, and 0.75 to 1.00 as excellent. The statistical significance level was set at 0.05. Statistical analysis was performed using SAS® version 9.2 for Windows® (SAS Institute Inc., Cary, NC).

Table 1 Upper boundaries conversion table from handprints to classified body area involvement scale in PASI and Low PASI scores in small involved areas.

	PASI	Low PASI			
HEAD					
Body area involved[a] (%)	0.1 – 0.9	0 - 0.25	0.26 - 0.5	0.6 - 0.75	0.76 - 0.9
Handprints	< 1	≤ 1/4	> 1/4 ≤ 1/2	> 1/2 ≤ 3/4	> 3/4 < 1
Area	**1**	**0.25**	**0.5**	**0.75**	**1**
UPPER EXTREMITIES					
Body area involved[a] (%)	0.1 – 1.9	0.1 - 0.5	0.6 - 0.75	0.76 - 1.5	1.6 - 1.9
Handprints	< 2	≤ 1/2	> 1/2 ≤ 3/4	> 3/4 ≤ 1 ½	> 1 ½ < 2
Area	0.1 – 0.9	**0.25**	**0.5**	**0.75**	**1**
TRUNK					
Body area involved[a] (%)	0.1 – 2.9	0.1 - 0.75	0.76 - 1.5	1.6 - 2.25	2.26 - 2.9
Handprints	< 3	≤ 3/4	> 3/4 ≤ 1 ½	> 1 ½ ≤ 2 ¼	> 2 ¼ < 3
Area	**1**	**0.25**	**0.5**	**0.75**	**1**
LOWER EXTREMITIES					
Body area involved[a] (%)	0.1 – 3.9	0.1 - 1	1.1 - 2	2.1 - 3	3.1 - 3.9
Handprints	< 4	≤ 1	> 1 ≤ 2	> 2 ≤ 3	> 3 < 4
Area	**1**	**0.25**	**0.5**	**0.75**	**1**

Area score of the classic PASI is classified into a four-point scale. Bold values represent used score system.

Results

Ten patients (five men and five women) participated in this study. The mean age was 41.4 years. The youngest patient was 18 years old and the oldest 65 years old. Table 2 shows the classic PASI scores and the Low PASI scores for the two investigators. The mean classic PASI score for investigator 1 was 4.33 (SD 2.06) and for the second investigator 4.14 (SD 2.37). The mean of the Low PASI scores for investigator 1 was 1.76 (SD 1.14) en for the second investigator 1.71 (SD 1.15).

The classic PASI scores of the two investigators ranged from 0.8 to 8.5, whereas the Low PASI scores ranged from 0.3 to 3.9. As can be seen in Table 2, one patient would have had a PASI of 8.5 using the classic PASI score, whereas this would be 3.9 using the Low PASI. Consequently, in this particular patient a difference of 4.6 in the score of the extent and severity of the disease was achieved by assessing the Low PASI.

Table 2 The observed PASI and Low PASI scores of each patient by investigator.

	PASI		Low PASI	
Patient	**Inv[a] 1**	**Inv[a] 2**	**Inv[a] 1**	**Inv[a] 2**
1	0.8	1.0	0.6	0.8
2	7.3	8.5	3.6	3.9
3	2.8	2.2	1.0	0.8
4	4.5	5.2	1.5	2.5
5	6.7	6.6	3.9	2.9
6	3.7	3.0	1.3	0.9
7	1.9	1.2	0.7	0.3
8	4.8	4.2	1.9	1.7
9	5.6	5.0	1.7	2.4
10	5.2	4.5	1.4	1.1
Mean	4.33	4.14	1.76	1.71
SD	2.06	2.37	1.14	1.15
Min	0.80	1.00	0.60	0.30
Max	7.30	8.50	3.93	3.93

SD: standard deviation.
[a] Inv: Investigator.

Table 3 The ICC and the mean differences between investigators of the PASI and the Low PASI, and between the methods of each investigator using a linear mixed model.

Methods	**ICC[a] (95% CI[b])** ***n*** **= 10**	**Differences (95% CI[b])**
PASI $_{inv1}$ – $_{inv2}$[c]	0.95 (0.82; 0.99)	0.19 (-0.30; 0.68)
Low PASI $_{inv1}$ – $_{inv2}$[c]	0.87 (0.56; 0.97)	0.05 (-0.37; 0.46)
PASI $_{inv1}$ - Low PASI $_{inv1}$[c]	0.74 (0.25; 0.93)	-2.57 (-3.44; -1.71)
PASI $_{inv2}$ - Low PASI $_{inv2}$[c]	0.75 (0.27; 0.93)	-2.43 (-3.37; -1.49)

Note that the Low PASI in these patients is by definition lower than the classic PASI.
[a] ICC: intraclass correlation coefficient; [b] CI: confidential interval; [c] Inv: investigator.

The ICC of interobserver agreement was excellent for both the classic PASI (ICC: 0.95 [95% confidence interval (CI): 0.82; 0.99)] and for the Low PASI [ICC: 0.87 (95% CI: 0.56; 0.97)]. However, the agreement between the methods is less [investigator 1: ICC: 0.74 (95% CI: 0.25; 0.93); investigator 2: ICC: 0.75 (95% CI: 0.27; 0.93)]. In addition, on average the classic PASI scores were statistically significantly higher than Low PASI scores (investigator 1: mean difference, -2.57 (95% CI: -3.44; -1.71); investigator 2: mean difference: -2.43 (-3.37; -1.49) (Table 3)).

Discussion

The Low PASI score showed a strong interobserver agreement for the measurement of affected body areas lower than 10%. Furthermore, it allows more possible scores at lower levels of psoriasis extent (affected areas lower than 10% in a body region) than the classic PASI. Although, this is a pilot study, these findings may have important implications for earlier achievement of treatment goals (achievement of PASI 75 / 90).[11]

In our study, the Low PASI scores were on average 2.5 lower compared to the classic PASI scores, especially for classic PASI scores higher than 4.2. As was mentioned earlier, several studies have emphasized the limitation of the PASI score in small areas; the score in the small areas might only change if the severity scores (erythema, induration and desquamation) change.[4-8] This limitation of the classic PASI score is the strength of the Low PASI score. The Low PASI score is able to measure and discriminate involved areas lower than 10% of a body region regardless changes in the severity scores.

Due to the lack of accuracy of the classic PASI score in the small areas, many authors attempted to modify or invent alternatives to replace the PASI score. These scores, however, were always based on new measurements (e.g. the PEASI and the PLASI) or the addition of extra measurements, such as quality of life assessments.[7,9,12,13] These changes imply that professionals have to alter their daily practice, and eventually it can lead to avoidance and problems with its implementation. On the contrary, the Low PASI does not pretend to substitute the classic PASI score, but to refine it in the small areas. Besides, we attempted to preserve all principles of the classic PASI. Therefore, our score is easy to learn and to use in daily practice.

As mentioned before, the patient that scored in the classic PASI 8.5 will get a score of 3.9 using the four-point scale for body areas involved lower than 10% of the Low PASI. This means a difference of 54.1% compared to the classic PASI. In daily practice, this difference may have consequences for treatment decisions.

Conclusion

The Low PASI score allows more possible scores at lower levels of psoriasis extent (affected areas lower than 10% in a body region) compared to the classic PASI. Especially, it could be a useful score for assessing the effectiveness of treatments. The PASI assessment in the lowest ranges becomes more and more important to represent differences between the treatments. In the present analysis, our sample size of 10 participants was sufficient to show differences between the absolute scores of the classic PASI and Low PASI in the lowest ranges. Therefore, the Low PASI adds important and relevant information to the classic PASI which could contribute to a better analysis of response to treatments.

To confirm the value of Low PASI in daily practice and in clinical studies, further studies should be focused on the validation of the Low PASI with a larger number of patients with mild-to-moderate psoriasis, the responsiveness to treatment and its stability over time.

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3.2

Comparison of the Dermatology Life Quality Index and the Children's Dermatology Life Quality Index in assessment of quality of life in patients with psoriasis aged 16-17 years

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Abstract

Background: Dermatology Life Quality Index (DLQI) and Children's Dermatology Life Quality Index (CDLQI) are widely used to assess quality of life (QoL) in adults (≥16 years) and children (4-16 years) with psoriasis. In the age group 16-17 years, it is not known whether DLQI and CDLQI reflect QoL impairment in the same way.

Objectives: To compare DLQI and CDLQI scores in patients with psoriasis aged 16-17 years.

Methods: Patients with psoriasis aged 16-17 years were asked to complete both the DLQI and CDLQI.

Results: Fifty-six patients were included. There was a high correlation between DLQI and CDLQI scores ($r = 0.90$, $P < 0.001$). The mean DLQI score (5.41 ± 5.20) was lower than the mean CDLQI (6.61 ± 5.74) ($P < 0.001$). The major part of this difference (Δ 0.61) was caused by the low score regarding sexual difficulties in the DLQI (0.11 ± 0.49) and the high score concerning sleep in the CDLQI (0.71 ± 0.93). In addition, the question related to sports scored 0.34 in the DLQI, but 0.86 in the CDLQI (Δ0.52). The question related to work/study in the DLQI scored lower than the question on school/holiday in the CDLQI (Δ0.41).

Conclusions: In patients with psoriasis aged 16-17 years, DLQI and CDLQI scores closely correlate, but the mean DLQI score was lower than the mean CDLQI score. This was caused primarily by differences in the answers to questions regarding sexual difficulties and sleep. As the QoL impacts experienced by people aged 16-17 may differ from those experienced by children or adults, QoL measures designed for use in this age range may have advantages over both child- and adult-specific measures.

Introduction

Psoriasis can have a negative impact on quality of life (QoL).[1-8] The Dermatology Life Quality Index (DLQI)[9,10] and the Children's Dermatology Life Quality Index (CDLQI)[11] are commonly used dermatology-specific QoL questionnaires in adults (≥16 years) and children (4-16 years) with psoriasis. As the lives and concerns of people with psoriasis aged > 16 years but < 18 years may differ from those of children or adults, it is not clear how best to measure their QoL.

Both the DLQI and the CDLQI are simple, self-administered questionnaires with the same total score range (0-30), consisting of 10 questions reflecting the impact of skin diseases on the patients' QoL over the last week.[10,12] Table 1 gives the individual questions. Six questions in both questionnaires are substantially the same, differing only slightly.[9,11] These questions concern itch, embarrassment, clothing, social or leisure activities, sports and problems caused by treatment [questions (Q) 1, 2, 4, 5, 6 and 10]. Four questions differ widely between the DLQI and CDLQI. In the DLQI these questions concern shopping or looking after the home or garden (Q3), work or study (Q7), problems with partners, close friends or relatives (Q8) and sexual difficulties (Q9). In the CDLQI the questions concern friendships (Q3), school and holiday (Q7), adverse comments (Q8) and sleep (Q9).

It is not known whether the DLQI and the CDLQI reflect QoL in the same way when used by people with psoriasis aged 16-17 years. Although the CDLQI is not validated for patients aged 17-18 years, the use of this questionnaire might provide additional information. The aim of this descriptive study was to examine and compare the way in which adolescents aged 16-17 years with psoriasis completed the DLQI and the CDLQI. This is important because the life issues that matter most to people of this age may not be fully captured by adult or children measures.[13]

Patients and methods

Study population and data collection

Data were extracted from the Child-CAPTURE (Continuous Assessment of Psoriasis Treatment Use Registry), a prospective, observational, longitudinal, daily clinical-practice pediatric psoriasis registry.[5] Since August 2011, patients aged 16 and 17 years were asked to complete both the DLQI and the CDLQI at the same visit. As part of the routine data collection for the clinical-practice pediatric psoriasis registry, all patients were given the same series of questionnaires in which the CDLQI was presented first. In the present study, all patients aged 16-17 years who completed both the DLQI and the CDLQI from September 2011 to October 2014 were included.

Outcome measures

Validated Dutch translations of the DLQI and the CDLQI (each with 10 questions; score range 0-30) were used.[14] Each question was scored on a four-point Likert scale from 0 to 3: 0, not at all/not relevant; 1, (only) a little; 2, (quite) a lot; 3, very much.[9-12] Higher scores indicate more impact on QoL.[9-12]

Analyses

The outcomes of all included patients were evaluated and described. SPSS version 20.0 for Windows (IBM, Armonk, NY, U.S.A) was used to calculate the characteristics of the patients. The Wilcoxon signed-rank test was used to compare the DLQI and CDLQI scores. The correlation coefficient between the DLQI and the CDLQI was calculated with the Pearson correlation test. *P*-values < 0.05 (two sided) were considered statistically significant.

As data were extracted from the Child-CAPTURE registry, the institutional review board considered this study in accordance with the applicable rules concerning the review of research ethics committees and informed consent.

Results

All patients agreed to participate. In total 56 patients (43% male) were included (Table 2). The mean age was 16.6 years. Patients attending the clinics were using topical therapy only (68% of all patients), systemic therapy (20%) or no therapy (13%).

Most and least affected topics in the questionnaires

The mean DLQI score (5.41 ± 5.20) was 1.20 points lower than the mean CDLQI (6.61 ± 5.74) ($P < 0.001$) (Table 1). The major part of this difference (Δ0.61) was caused by the low score regarding sexual difficulties in the DLQI (0.11 ± 0.49) and the high score concerning sleep in the CDLQI (0.71 ± 0.93). In addition, the question related to sports (present in both questionnaires) scored 0.34 in the DLQI but 0.86 in the CDLQI (Δ0.52). The question related to work/study in the DLQI scored lower than the question on school/holiday in the CDLQI (Δ0.41).

In the DLQI, the question topics with the highest mean scores were itch (1.18 ± 0.92), embarrassment (0.88 ± 0.92), clothing (0.71 ± 0.97) and problems with treatment (0.71 ± 0.95). In the CDLQI the question topics with highest mean scores were itch (1.18 ± 0.92), embarrassment (0.86 ± 1.0), sports (0.86 ± 1.09), school/ holiday (0.86 ± 0.88) and problems with treatment (0.84 ± 0.85). In contrast, the DLQI questions related to sexual difficulties (0.11 ± 0.49) and to shopping or looking after the home or garden (0.27 ± 0.62) scored lowest. The lowest-scoring questions in the CDLQI concerned friendships (0.07 ± 0.26) and adverse comments (0.30 ± 0.60).

Table 1 Individual question scores for the Dermatology Life Quality Index (DLQI) and Children's Dermatology Life Quality Index (CDLQI).

Question	DLQI	CDLQI	DLQI score *n* = 56	CDLQI score *n* = 56
Total			5.41 ± 5.20	6.61 ± 5.74
1	Itch/pain	Itch/pain	1.18 ± 0.92	1.18 ± 0.92
2	Embarrassment	Embarrassment	0.88 ± 0.92	0.86 ± 1.0
3	Shopping/ looking after home or garden	Friendships	0.27 ± 0.62	0.07 ± 0.26
4	Clothing	Clothing	0.71 ± 0.97	0.59 ± 0.89
5	Social or leisure activities	Going out/playing/doing hobbies	0.46 ± 0.66	0.34 ± 0.64
6	Sports	Swimming/sports	0.34 ± 0.61	0.86 ± 1.09
7	Work/study	School/holiday	0.45 ± 0.87	0.86 ± 0.88
8	Problems with partners/close friends/ relatives	Teasing/bullying/ asking questions/ avoiding	0.30 ± 0.60	0.30 ± 0.60
9	Sexual difficulties	Sleep	0.11 ± 0.49	0.71 ± 0.93
10	Treatment	Treatment	0.71 ± 0.95	0.84 ± 0.85

Values are the mean ± SD. The possible score range for each individual question of the DLQI and CDLQI is 0-3.

Correlation between Dermatology Life Quality Index and Children's Dermatology Life Quality Index scores

Figure 1 shows the relationship between the individual DLQI and CDLQI scores (correlation = 0.90, $P < 0.001$).

Score descriptor banding of the Dermatology Life Quality Index and Children's Dermatology Life Quality Index

The mean scores for the DLQI (5.41) and the CDLQI (6.61) were both at the borderline between the relevant score band descriptors of 'small effect on QoL' and 'moderate effect on QoL' (Table 3). In 15 of the 56 patients (27%) the DLQI was interpreted as there being

Table 2 Patient characteristics ($n = 56$).

Patient characteristic	Value
Age (years), mean (range)	16.6 (16-17)
Sex male, *n* (%)	24 (43)
Prescribed treatment, *n* (%)	
Topical	38 (68)
Systemic	11 (20)
With additional topical therapy	7 (13)
No additional topical therapy	4 (7)
None	7 (13)

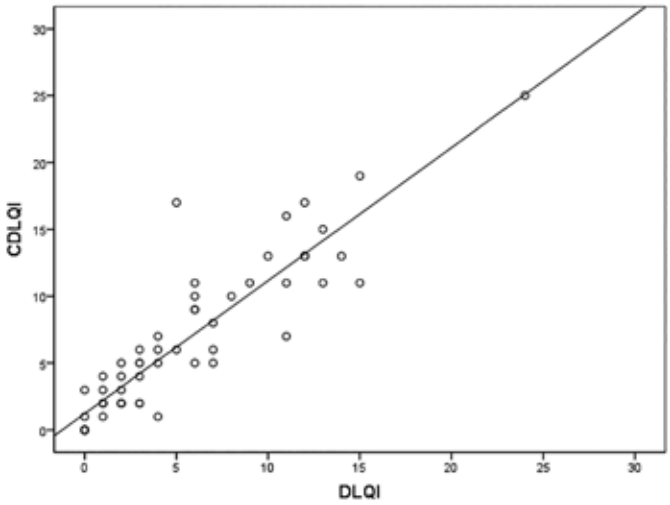

Figure 1 Correlation between Dermatology Life Quality Index (DLQI) and Children's Dermatology Life Quality Index (CDLQI) scores.

Correlation = 0.90, $P < 0.001$.

no effect on the patient's life (band 0, score 0-1), whereas the impact was observed as small (band 1, score 2-5), moderate (band 2, score 6-10), very large (band 3, score 11-20) and extremely large (band 4, score 21-30) in 32%, 20%, 20% and 2%, respectively.

Table 3 Headings and banding descriptors for the Dermatology Life Quality Index (DLQI) and the Children's Dermatology Life Quality Index (CDLQI).

	DLQI		CDLQI
Headings			
	Symptoms and feelings (Q1-2)		Symptoms and feelings (Q1-2)
	Daily activities (Q3-4)		Leisure (Q4-6)
	Leisure (Q5-6)		School or holidays (Q7)
	Work and school (Q7)		Personal relationships (Q3,8)
	Personal relationships (Q8-9)		Sleep (Q9)
	Treatment (Q10)		Treatment (Q10)
Bandings			
0	0-1	No effect	0-1
1	2-5	Small effect	2-6
2	6-10	Moderate effect	7-12
3	11-20	Very large effect	13-18
4	21-30	Extremely large effect	19-30

However, for the CDLQI the impact was interpreted as none (band 0, score 0-1), small (band 1, score 2-6), moderate (band 2, score 7-12), very large (band 3, score 13-18) and extremely large (band 4, score 19-30) in 18%, 43%, 21%, 14% and 4% of the patients, respectively (Figure 2).

With both the DLQI and the CDLQI, approximately 60% of patients were in band 0 or 1. However, in band 0 the percentage (27%) of DLQI subjects was higher than the percentage of CDLQI subjects, and in band 1, the percentage (43%) of CDLQI subjects was higher than the percentage of DLQI subjects.

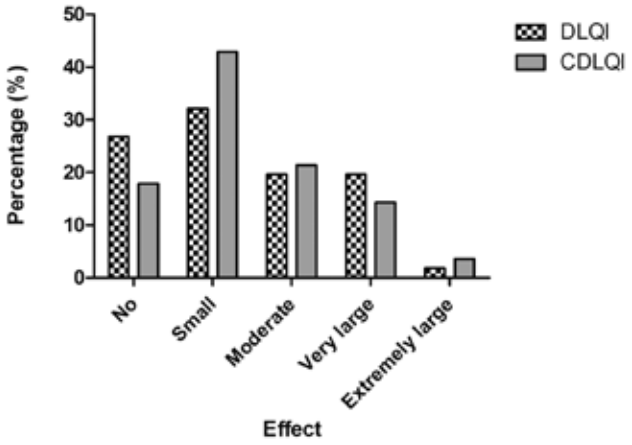

Figure 2 Score descriptor banding of the Dermatology Life Quality Index (DLQI) and Children's Dermatology Life Quality Index (CDLQI).

Discussion

In our study, in which only patients aged 16-17 years with psoriasis were included, the mean total DLQI score was 1.2 points lower than the mean total CDLQI score. The major part of this difference was due to Q9, which is related to sexual difficulties in the DLQI. In the CDLQI this question concerns sleep (Δ0.61). In the DLQI the mean score of the sexual difficulties question was the lowest for all questions (0.11), whereas the sleep question in the CDLQI scored highly (0.71). Sexual issues could be important to some people with psoriasis aged 16-17 years; however, it is unknown whether the low mean score implied that the subjects experienced few sexual difficulties, whether this item was not relevant for them, or whether embarrassment and/or the presence of a parent during questionnaire completion influenced their answers.

The high-scoring CDLQI question regarding sleep is clearly relevant for this age group. Sleep impairment has been reported in a cohort of 125 children with psoriasis, of which a subgroup was aged 16-17 years old.[5] Sleep impairment has also been described in adults with psoriasis.[15-17] Sleep problems because of psoriasis are more likely to persist over a lifetime in patients with earlier age of disease onset.[18] Some QoL instruments incorporate a question related to sleep,[15,17] although not the DLQI. If patients aged 16 years and above complete only the DLQI[9], the impact of their psoriasis on their sleep is not highlighted, even though it is possible that some aspects of the results of sleeping poorly, such as the impact on work or study, may be reflected in the answers to other questions.

When choosing which questionnaire to use to measure QoL in this age group, consideration should be given to whether or not the instrument incorporates a question concerning sleep.

The question concerning work/study in the DLQI scored remarkably lower (Δ0.41) than the question relating to school/holiday in the CDLQI. It seems that the concepts of school and holiday are more appropriate than work and study for this age group. In the Netherlands, most people start their higher education 'study' after the age of 18 years, and only a minority of 16-17 year olds have paid employment.

Although a similar question (Q6) concerning sports occurs in both the DLQI and the CDLQI, there was a considerable difference in the way this question was scored, with the CDLQI question scoring much higher (Δ0.52). This might be caused by the additional word 'swimming' in the CDLQI question. Swimming may be an important activity at this age, or the word swimming may give rise to other associations.

It is remarkable that low scores were recorded for effects on friendships. This may reflect that the question relates more to established friendships than meeting new people, which is likely to be much more of an issue in this age group.

In a recent study in which the DLQI was completed by 192 patients aged 16-91 years with 20 different skin conditions, the most affected topics were the items 1, 2 and 4 regarding physical symptoms, embarrassment and impact on clothes, whereas the least affected topic was Q9 on sexual difficulties.[19] These findings are in accordance with our results.

As the QoL impacts experienced by subjects aged 16-17 years may differ from those experienced by children or adults,[13] QoL measures designed for use in this age range may have advantages over both child- and adult-specific measures. Some specific instruments to assess QoL in adolescents with skin diseases have already been developed (e.g. the Skindex-Teen[20] and T-QoL).[21] Indeed, the Skindex-Teen[20] incorporates more items in the psychosocial functioning domain, and T-QoL[21] includes eight questions on self-image and six questions on psychological impact. These measures may therefore be more sensitive for this specific age group than either the DLQI or CDLQI. Also, acne-specific measures (e.g. the Cardiff Acne Disability Index, CADI),[14] were designed for use in this age group. To our knowledge, psoriasis-specific QoL instruments designed for use in patients 16-17 years are lacking.

In our study the mean total DLQI was 1.20 points lower than the mean total CDLQI. This difference was minor compared with the minimal clinically important difference (MCID) (score change = 4.0) for the DLQI.[19] Therefore, although this study has focused on differences in the scoring between the DLQI and CDLQI, it is reassuring that there is such a close correlation between the overall scores, with the difference between the means being well below the MCID for the DLQI. So far, data on the MCID for the CDLQI are not available. In 2005, a score descriptor banding system was established to improve the clinical interpretation of the DLQI (Table 3).[10,22] Comparable score descriptor bands were

suggested for the CDLQI, but these data have been published only as an abstract; the detail of their validation is therefore not known.[12,23]

In this study, the percentage of patients in band 1 was highest in both the DLQI and the CDLQI, corresponding to a small effect on a patient's life. Whereas for the DLQI the percentage of patients was higher in band 0, for the CDLQI this percentage was higher in band 1 (Figure 2). This suggests that when patients with psoriasis experience lower levels of QoL impact, this is detected more successfully by the CDLQI. However, in band 3, corresponding to a very large effect on a patient's life, the percentage of patients was higher for the DLQI than for the CDLQI. It would be interesting to understand from the patients' perspective whether in their view the DLQI or CDLQI scores best reflect their experience. However, as this study reports data collected routinely in the clinic for a daily clinical-practice pediatric psoriasis registry it was not possible to address this.

The close correlation between the two measures does give some reassurance in the context of those studies that have used the CDLQI in subjects aged 17-18 years. Although the CDLQI was not originally designed for or validated in this age range, the scores and associated score meaning bands recorded in this study are appropriate in the context of the parallel DLQI scores, and may even be more sensitive in detecting low levels of impact.

The data reported are based on questionnaires that had been collected routinely for the clinical-practice pediatric psoriasis registry. As this was not a prospective study there was not the opportunity to present the CDLQI and DLQI in random order. It is possible that routinely presenting the CDLQI for completion before the DLQI may have biased the DLQI completion.

In conclusion, in patients with psoriasis aged 16-17 years, the DLQI overall scored lower than the CDLQI. This was caused primarily by differences in the answers given to the questions regarding sexual difficulties (low score in the DLQI) and sleep (high score in the CDLQI). In addition, the question related to sports (present in both questionnaires) revealed a remarkable difference, with lower scores in the DLQI. The question related to work/study in the DLQI scored lower than the question on school/holiday in the CDLQI. Neither the DLQI nor the CDLQI are specifically designed for people aged 16-17 years, but up to now it has not been clear how these questionnaires perform comparatively in this age group. In studies designed to assess QoL in this specific age group, consideration should be given to using measures validated specifically for patients of these ages.

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3.3

Validation of the Simplified Psoriasis Index (SPI) in children and adolescents with psoriasis

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Submitted

Abstract

Background: The Simplified Psoriasis Index (SPI) is a three-domain assessment measure for psoriasis, including separate indicators of current severity (SPI-s), psychosocial impact (SPI-p), and past history and interventions (SPI-i). There are two complementary versions available designed for completion by a health professional (proSPI) or by patient self-assessment (saSPI). The validity and reliability of proSPI versus saSPI have already been demonstrated in adults. To date, validated severity measures for pediatric psoriasis do not exist.

Objective: To validate the current severity (SPI-s) and psychosocial impact (SPI-p) domains of proSPI and saSPI in children and adolescents with psoriasis.

Methods: All patients <18 years with psoriasis visiting the dermatology outpatient department of the Radboud university medical center in the Netherlands between September 2013 and April 2014 were asked to complete Dutch versions of saSPI and the Children's Dermatology Life Quality Index (CDLQI). The original English versions of proSPI and PASI (Psoriasis Area and Severity Index) were completed by the physician at the same visit.

Results: 113 patients (median age 12.0, range 4-17 years) were included. There was a close correlation between proSPI-s and PASI ($r = 0.87$), which was higher than that between saSPI-s and PASI ($r = 0.69$). The correlation between SPI-p and CDLQI was 0.78. The full range of scores was utilized in both proSPI-s and SPI-p, although the highest saSPI-s score was 30 (maximum 50).

Conclusions: In pediatric psoriasis, proSPI and saSPI are shown to be valid and usable. SPI-s and SPI-p can be readily introduced into routine clinical practice.

Introduction

Psoriasis is a common chronic inflammatory skin disorder which can have a major negative impact on quality of life (QoL).[1,2] For optimal therapeutic decision-making, it is essential to have valid and reliable clinical measures to assess psoriasis severity and its impact on patients' lives as precisely as possible. In about one third of patients, psoriasis starts before adulthood.[3] In pediatric psoriasis, the most widely used measures for assessing disease severity and QoL are the Psoriasis Area and Severity Index (PASI)[4] and the Children's Dermatology Life Quality Index (CDLQI)[5] respectively. The CDLQI has been validated in children aged between 4 and 16 years[5], whereas validation of PASI in children and adolescents has never been performed.

The Simplified Psoriasis Index (SPI) is a three-domain assessment measure for psoriasis, including separate indicators of current severity (SPI-s), psychosocial impact (SPI-p), and past history and interventions (SPI-i).[6,7] The first domain, SPI-s (range 0-50), is calculated by multiplying a composite psoriasis extent score (range 0-10) by an overall average severity score (range 0-5).[6] The former is derived using a three-point scale (0, absent or minimal; 0.5, noticeable; 1, extensive) to allocate a psoriasis extent score to each of ten body areas, with extra weight given to the scalp, face, hands, feet and anogenital skin in order to reflect their greater functional and psychosocial impact.[6] The second domain, SPI-p, records the psychosocial impact of psoriasis as a Likert scale (0-10) derived from the patient's (or parent's) marking of a 10-cm visual analogue score line.[6] The third domain, SPI-i, comprises four questions about disease course and six about previous interventions received.[6] Detailed information is described by Chularojanamontri et al.[6] The original SPI proformas are freely available for download.[6]

SPI is available in two complementary versions, enabling it to be completed either by health professionals (proSPI) or by patients using a simplified self-assessment proforma (saSPI).[6,7] The validity and reliability of proSPI and saSPI have been demonstrated in adults.[6] To date, validated severity measures for pediatric psoriasis do not exist. This study was designed to investigate the criterion validity, construct validity and response distribution[6] of SPI-s and SPI-p in both the professional and the self-assessment versions of SPI in a Dutch population of children and adolescents (<18 years of age) with psoriasis.

Methods

Criterion validity, construct validity and response distribution

We used the same methodology for defining and assessing validity as were used in the original publication by Chularojanamontri et al.[6]

Criterion validity compares the extent to which a measure relates to a gold standard.[6,8] We used PASI and CDLQI as the standards against which to measure SPI-s and SPI-p respectively by investigating the correlations between:

a) proSPI-s and PASI
b) saSPI-s and PASI
c) SPI-p and CDLQI

Construct validity measures the extent to which an instrument relates to other measures.[6,8] The relationships between the three psoriasis severity scores and the two psychosocial impact scores were investigated as follows:

a) proSPI-s, saSPI-s, and PASI versus CDLQI
b) proSPI-s, saSPI-s, and PASI versus SPI-p

Response distribution measures whether the entire range of a scale is used.[6,8] We examined the response distributions of proSPI-s, saSPI-s and SPI-p.

Study population and data collection[6]

From September 2013 to April 2014 all children and adolescents <18 years with psoriasis attending the dermatology outpatient department at the Radboud university medical center in the Netherlands were asked to complete saSPI and CDLQI. The order in which patients filled out the questionnaires was random. A photographic image key with several examples of psoriasis severity[6] was attached to the saSPI. At the same visit, proSPI and PASI were completed by author MJvG who was familiar with PASI-scoring but not with SPI. The proSPI and saSPI scores were collected as part of the routine data collection for a daily clinical practice pediatric psoriasis registry, the Child-CAPTURE (Continuous Assessment of Psoriasis Treatment Use Registry).[2] The present study was considered by the institutional review board in accordance with the applicable rules concerning the review of research ethics committees and informed consent.

Assessment tools

Simplified Psoriasis index

Detailed description on the original development and contents of the validated SPI in adults is described by Chularojanamontri et al.[6] The proSPI-s and proSPI-p proforma used in this study was identical to the one described in adults.[6] The saSPI-s and saSPI-p, were however, slightly modified with the agreement of the original authors to make the proforma more easily understood by children (and/or their parents). The modified saSPI proforma was then translated into Dutch. Children were allowed to get help in completing saSPI from their parent and/or guardian.

CDLQI

To quantify the psychosocial impact of psoriasis a validated Dutch translation of the CDLQI was used as the reference standard.[5,9] The CDLQI is a commonly used dermatology-specific QoL self-administered questionnaire in children including ten questions (score range 0-30).[5] Higher scores indicate more impact on QoL.[5]

PASI

PASI was used to assess the extent and severity of psoriasis (score range 0-72).[4]

Analyses

All proSPI and saSPI proformas with one or more missing values were excluded. SPSS® version 22.0 for Windows® (SPSS Inc., Chicago, IL, U.S.A) was used to perform the statistical analyses. Correlation coefficients were calculated using two-tailed Spearman's correlation coefficients with values of >0.8, 0.5-0.8, and <0.5 indicating a good, average and poor correlation respectively.[6,10]

Results

Patient characteristics

In total 113 patients with psoriasis (54.9% female) were included, whereas 10 patients were excluded because of one or more missing values. Median age was 12.0 years with a range between 4 and 17 years. In most of the patients (72.6%) disease onset was before age 10. Median PASI was 4.0 (range 0-19.9), while median CDLQI was also 4.0 (range 0-23).

Criterion validity (Table 1): proSPI-s was closely correlated with PASI (r = 0.87). Correlation between saSPI-s and PASI was lower (r = 0.69). The correlation between SPI-p and CDLQI (r = 0.78) indicated that SPI-p was a valid summary measure of QoL impairment in children and adolescents.

Construct validity (Table 1): saSPI-s was moderately correlated with SPI-p (r = 0.68) and CDLQI (r = 0.64). This correlation was higher than the correlations between the two psychosocial impact measures and either PASI (PASI vs. SPI-p: r = 0.40; PASI vs. CDLQI: r = 0.39) or proSPI-s (proSPI-s vs. SPI-p: r = 0.43; proSPI-s vs. CDLQI: r = 0.44).

Response distribution: A wide range of scores was obtained for all measures, although saSPI-s scores >30 were not utilized: the median proSPI-s and saSPI-s scores were 3.0 (range 0-50) and 3.5 (range 0-30) respectively (Figure 1). Median SPI-p was 3.0 (range 0-10).

Table 1 The correlation between proSPI-s, saSPI-s, PASI, SPI-p and CDLQI in 113 children and adolescents aged <18 years with psoriasis.

Spearman rank correlation coefficients	proSPI-s	saSPI-s	PASI	SPI-p	CDLQI
proSPI-s	-	0.67	**0.87**	0.43	0.44
saSPI-s	0.67	-	0.69	0.68	0.64
PASI	**0.87**	0.69	-	0.40	0.39
SPI-p	0.43	0.68	0.40	-	**0.78**
CDLQI	0.44	0.64	0.39	**0.78**	-

proSPI-s, severity component of the professional Simplified Psoriasis Index; saSPI-s, severity component of the self-assessment Simplified Psoriasis Index; SPI-p, psychosocial impact component of the Simplified Psoriasis Index; PASI, Psoriasis Area and Severity Index; CDLQI, Children's Dermatology Life Quality Index.

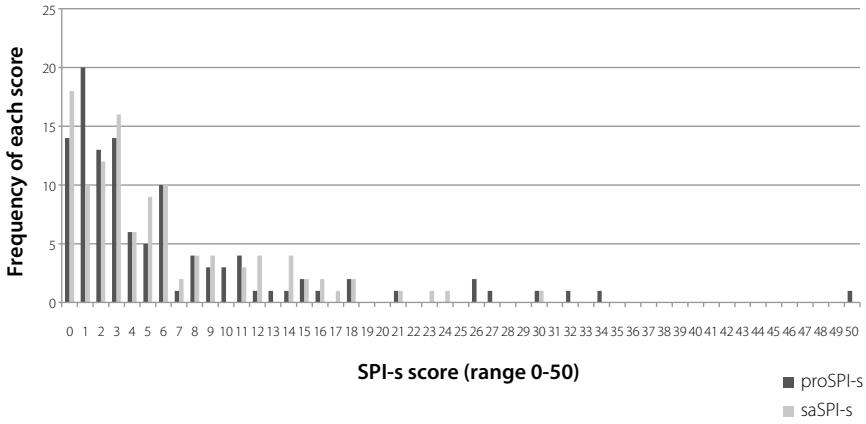

Figure 1 The response distributions of proSPI-s and saSPI-s in 113 patients.

SPI, Simplified Psoriasis Index; proSPI-s, severity component of the professional Simplified Psoriasis Index; saSPI-s, severity component of the self-assessment Simplified Psoriasis Index.

Discussion

This study has shown that both the professional and self-assessment versions of SPI are valid assessment tools and suitable for routine clinical use in documenting psoriasis severity and psychosocial impact in children and adolescents. Our findings are similar to those reported in adults,[6] with a close correlation between proSPI-s and PASI ($r = 0.87$) and a rather lower correlation between saSPI-s and PASI ($r = 0.69$). The correlation between SPI-p and CDLQI ($r = 0.78$) was satisfactory, although somewhat lower than that reported between SPI-p and Dermatology Life Quality Index (DLQI) in adults ($r = 0.89$).[6]

Valid and reliable severity measures are essential in order to plan and monitor psoriasis therapy optimally. Although there are many psoriasis severity measures available for use in adults, none was found to be adequately validated and no best instrument was identified in a systematic review published in 2010.[7,8] The authors of the review did, however, suggest that, as PASI was the most commonly reported measure in research publications, it permitted some comparison of results from clinical trials.[8] Neither PASI nor any other psoriasis measure has ever been validated in children.

It is important to note the differences between PASI and SPI-s. The latter dispenses with the need to estimate body surface area involvement and replaces it with a three option choice for each of its ten body areas.[6] Furthermore, the added weight given to functionally or psychosocially important body sites such as the face, scalp and hands enables SPI-s to capture areas of involvement which cannot be adequately represented by PASI.[6] Complete agreement between PASI and SPI-s is not to be expected. We chose PASI, however, as the best available reference standard for psoriasis severity against which to validate SPI-s. [6-8,11] To our knowledge, SPI-s is now the first validated severity measure for pediatric psoriasis.

An advantage of SPI over other psoriasis assessment measures is that the SPI includes a self-assessment version (saSPI), which can provide valuable insight into patients' perceptions of their disease, whether they be adults or children, particularly where saSPI and proSPI scores diverge.[6] The correlation between saSPI-s and PASI in our pediatric population ($r = 0.69$) was essentially the same as that observed in an adult population ($r = 0.70$) with a closer correlation between severity and psychosocial impact (SPI-p and CDLQI) when scored by patients using saSPI-s rather than by health professionals using proSPI-s or PASI in both studies.[6]

Apart from saSPI, there are few patient-administered psoriasis severity measures for adults:[8,11,12] they include the Self-Administered PASI (SAPASI)[13,14], the Patient Report of Extent of Psoriasis Involvement (PREPI)[15] and the Patient's Global Assessment (PaGA).[8] Of these, to the best of our knowledge, only SAPASI has been compared with PASI. The correlation between PASI and SAPASI has been described as moderate to good in adults, with correlation rates similar to those between PASI and saSPI-s in our study of children and adolescents.[8,11-14,16-22] It is, however, complex to use, requiring a professional to

estimate body surface area involvement from the patient's sketches.[23] We have been able to show that saSPI-s is a valuable quantitative patient self-assessment measure of disease severity for children and adolescents with psoriasis.

It has to be noted that the photographic image key illustrating grades of psoriasis severity as a guide to scoring saSPI-s for adults[6] was not developed for use in children. We observed that children found these images disturbing; however, a visual guide to distinguish the different severity grades might be of added benefit, especially for children, perhaps utilizing a computer-generated 3d graphic doll mannequin.

In addition to the clinical severity measures discussed above, SPI includes a psychosocial impact component (SPI-p).[6] In our pediatric population SPI-p was closely correlated with CDLQI ($r = 0.78$), which is in line with the correlation between SPI-p and DLQI in adults ($r = 0.89$).[6] SPI-p could be simply and rapidly obtained in children and adolescents, though, in contrast to CDLQI[5], it gives the professional no specific information on which aspects of QoL are impaired.

As noted above, it is noteworthy that both psychosocial impact measures (SPI-p and CDLQI) were more closely correlated with saSPI-s than with the other two severity parameters (proSPI-s and PASI), as was observed in adults by Chularojanamontri et al. This suggests that both adults and children are influenced by the psychosocial impact of their disease when scoring their disease severity.[6]

The original SPI as described by Chularojanamontri et al.[6] includes a third domain (SPI-i) intended to capture summary information about past history and interventions received. Initially, a slightly modified version of SPI-i was incorporated into the proforma given to patients and parents. We found, however, that this was difficult and time-consuming for them to complete and added little information which we did not already know. We therefore decided to remove this domain from our pediatric version of SPI.

In conclusion, it is reassuring that there is such concordance between our pediatric psoriasis data and the validated data described in adults.[6] Although we feel that our modified children's SPI can be readily introduced into clinical practice and provides a simple and valuable way of assessing and monitoring psoriasis in children and adolescents, further studies are needed to determine the suitability of the pediatric version of SPI for use in clinical trials as well as in routine clinical practice.

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Chapter 4

Summary, discussion and main conclusions

In the summary and discussion below, all aims of the thesis will be separately summarized, addressed and discussed. In addition, main conclusions of this thesis will be formulated.

Treatments

Aim 1: To investigate prospectively the effectiveness, safety and influence on quality of life of calcipotriol/ betamethasone dipropionate ointment in pediatric psoriasis in daily clinical practice.

In **Chapter 2.1** we provided a prospective, daily clinical practice study on the effectiveness, safety and influence on quality of life (QoL) of calcipotriol/betamethasone dipropionate ointment in 73 children and adolescents with psoriasis. Median treatment duration was 35 weeks (range 1-176). At week 12, mean Psoriasis Area and Severity Index (PASI) was slightly improved from 5.2 to 4.4 (15.4%), whereas at week 24 its effect was maintained (PASI 4.3, 17.3% improvement). Patients who were assigned to the more intensive treatment regimen (prescription of the ointment for once-daily use for four weeks, thereafter once daily four times per week) started with higher baseline PASI scores and revealed more improvement in PASI than patients who were prescribed the less intensive treatment regimen (starting directly with once-daily application four times per week). At week 12, median Children's Dermatology Life Quality Index (CDLQI) significantly improved from 5.5 at baseline to 4.0 and visual analogue scale (VAS) scores for pain and itch declined. In five patients (7%) possible treatment-related adverse events (AEs) were described of which four patients had striae. Related serious adverse events (SAEs) did not occur.

To the best of our knowledge, studies on the use of this two-compound *ointment* in pediatric psoriasis are lacking. However, three recent studies were published on the use of calcipotriol/ betamethasone dipropionate *gel* to treat pediatric scalp psoriasis.[1-3] One of these studies described a prospective, daily clinical practice cohort of pediatric psoriasis patients aged 4-17 years (84 treatment episodes) and demonstrated significant improvements in Psoriasis Scalp Severity Index from 18.7 ± 11.8 to 12.7 ± 9.4 in the first 12 weeks. Its effect was maintained through 48-weeks follow-up. Striation of the skin was reported in three patients (4.1%).[1] The other two studies were both phase II, prospective, open-label, multicenter, single-arm, eight-week studies in respectively 78[2] and 31[3] adolescents with scalp psoriasis (aged 12-17 years) with safety as the primary endpoint. AEs, which were mostly mild, were reported in 35%[2] and 52%[3] of the patients respectively.[2-4] Neither clinically relevant changes in parameters of calcium metabolism nor SAEs were observed.[2-4] Direct comparison, however, between our data on the two-compound *ointment* and these studies on the formulation in *gel* vehicle to treat scalp psoriasis, is not possible due to differences in assessment measures, treatment regimens, and the used vehicle.

The adherence to treatment in the two multicenter, eight-week trials on the use of the two-compound *gel* was reasonably high.[2-4] Due to the daily clinical practice design of

our study, we did not measure treatment adherence. Adherence to topical treatments in psoriasis and other skin diseases is known to be poor[5-9], especially in adolescents.[2,3,5,10,11] One of many strategies to improve treatment adherence is the scheduling of early and more frequent follow-up visits[5-7,12-14], which might induce better treatment outcomes.[7,15] As the return visits in our daily clinical practice study were variable and not scheduled to drive adherence, treatment adherence was probably lower than reported in the eight-week trials. In addition, the follow-up time was much longer in our study, which is not driving adherence too. It is also known that treatment adherence can be influenced by the kind of vehicle used[3,5,7,16,17] and that adult psoriasis patients preferred the two-compound *gel* to the *ointment* in real life clinical practice, as it was more convenient, easier to use, and faster to apply.[15] However, whether pediatric patients prefer the *gel* to the *ointment* has not been investigated yet. The fact that we used an ointment in our study might have negatively influenced adherence. At the moment, an international, multicenter, prospective, open-label, non-controlled, single-group, four-week trial on the safety and efficacy of once-daily topical treatment with the two-compound formulation in *aerosol foam* in adolescents (aged 12 < 17 years) with plaque psoriasis is in the developmental pipeline.[18] Theoretically, it may well be that in adolescents with body and scalp plaque psoriasis this aerosol foam will be preferred due to its less greasy and messy vehicle.[4,19,20] Hopefully, this new vehicle will improve adherence and therefore, indirectly, improve clinical outcomes.

In our study AEs were addressed by the patient and/or parent or noticed by the physician. As striae distensae are commonly observed in adolescents, particularly with rapid growth spurts[21,22] and obesity,[22,23] and a control group was lacking, a conclusion on the (relative small) number of striae in our study was not possible. Due to its daily clinical practice design, routine laboratory tests and urine analyses to detect systemic absorption were not performed. Ideally, it would be interesting to investigate the effects on the hypothalamic-pituitary-adrenal (HPA) axis and calcium metabolism. Fortunately, at the moment, there are two upcoming trials investigating the safety and effects of the two-compound product in *gel* and *aerosol foam* vehicle respectively on HPA axis and calcium metabolism in adolescents (aged 12 < 17 years) with psoriasis.[18,24]

In conclusion, it is very important to obtain data from a daily clinical practice setting in addition to the information provided by randomized controlled trials (RCTs). Although RCTs will include scheduled follow-up visits to drive adherence and will assess the effects on HPA axis and calcium metabolism, advantages of daily clinical practice data include the possibility to provide long-term data and to reveal information on patients not strictly fitting the inclusion criteria of RCTs.[25] Therefore, daily clinical practice data will probably reflect real-life treatment practice more precisely.

Aim 2: To present a systematic overview on the efficacy and safety of systemic treatments in pediatric psoriasis.

and

Aim 3 and 4: To investigate prospectively the effectiveness, safety and the influence on quality of life of methotrexate (aim 3) and fumaric acid esters (aim 4) in pediatric psoriasis in daily clinical practice.

In **Chapter 2.2** we presented a systematic evidence-based update of the literature on efficacy and safety of all systemic treatments in pediatric psoriasis until March 2014. Regarding the conventional systemic treatments, most data were available on methotrexate (MTX), although the evidence was retrospectively collected and of low level. New was the evidence on fumaric acid esters (FAE), albeit retrospectively collected in a low number of patients. Of all systemic treatments, etanercept has accumulated most evidence, demonstrating maintained efficacy and reassuring safety through 96 weeks.[26] Overall, the available evidence on efficacy and safety of systemic treatments in pediatric psoriasis was concluded to be limited as prospective studies were scarce and most studies had low level of evidence. In addition, apart from 96-weeks safety and efficacy data on etanercept, long-term safety data were lacking.
Because the evidence on the conventional systemic treatments was still sparse, we decided to analyse daily clinical practice data from our prospective Child-CAPTURE registry on the use of MTX **(Chapter 2.3)** and FAE **(Chapter 2.4)** in children and adolescents with psoriasis.

In **Chapter 2.3** we investigated prospectively the effectiveness, safety and the influence on QoL of MTX in 25 pediatric psoriasis patients in daily clinical practice. Treatment duration ranged from 12.6 to 163.4 weeks, with a median of 60.4 weeks. Rates of PASI 75 were achieved in 4.3%, 33.3%, 40% and 28.6% of patients at week 12, 24, 36 and 48, respectively. Median PASI improved from 10.0 (range 3.8-42.4) at baseline to 4.3 (range 0-19.8) at week 24, whereas median CDLQI decreased from 9 (range 2-20) to 3.8 (range 0-21). MTX seemed to have a reasonable safety profile with severe nausea ($n = 5$), infections requiring antibiotics or antiviral medication ($n = 5$) and severe tiredness ($n = 4$) as most frequently reported AEs of interest. The only reported SAE was hospitalization because of pneumonia which resolved without sequelae.

This study was the first to present prospective data in the literature on the effectiveness, safety and influence on QoL of MTX in children and adolescents with psoriasis. Based on our clinical impression of the effectiveness of MTX before analysing our Child-CAPTURE data, we were somewhat disappointed by the results of our own study. Very recently however, more or less similar effectiveness data were found in a prospective, multicenter, randomized, double-blind trial which investigated the safety

and efficacy of two doses of adalimumab (0.4 mg/kg up to 20 mg and 0.8 mg/kg up to 40 mg) versus MTX in 114 pediatric patients with severe chronic plaque-type psoriasis.[27-29] Thirty-seven patients (mean age 13.4 years) were treated with MTX (0.1-0.4 mg/kg weekly up to 25 mg/week) for 16 weeks.[28] PASI 75 was achieved in 32.4% of patients at week 16. AEs occurred in 75.7% of patients of which 54.1% infections, whereas deaths, serious infections, malignancies or SAEs did not occur.[27,28] Direct comparison, however, is difficult as effectiveness data were presented at different time points (week 16 in the RCT[28] and week 12 and 24 in our study). Despite the higher baseline PASI in the RCT (mean 19.2, SD 10.0)[28] compared to our study (median 10.0, range 3.8-42.4) effectiveness results were, however, in the same range.

The other conventional systemic treatment we decided to gather more evidence on was FAE. In **Chapter 2.4** we described a prospective daily clinical practice case series on 14 children and adolescents with recalcitrant plaque-type psoriasis treated with FAE. FAE (mean treatment duration 48.6 weeks, range 12-124) resulted in an improvement of psoriasis severity and QoL in the majority of children. Mean PASI (±SEM) improved from 10.5 (1.0) at baseline to 8.6 (1.1), 6.2 (1.6) and 4.9 (1.5) at week 12, 24 and 36, whereas mean CDLQI (±SEM) improved from 8.9 (1.4) at baseline to 6.8 (1.2), 3.7 (1.4) and 3.1 (2.0), respectively. Although side effects occurred frequently, they were usually mild and transient. Most frequently reported side effects were gastrointestinal complaints (n = 13, 92.9%) and flushing (n = 10, 71.4%), whereas lymphocytopenia (n = 5, 45.5%) and eosinophilia (n = 4, 36.4%) were most commonly observed laboratory abnormalities. One SAE, unrelated to FAE, was reported.

Last month, a retrospective, non-interventional, multicenter study in Germany (KIDS FUTURE study) on the efficacy and safety of FAE treatment in 127 children and adolescents (aged 6-17 years) with psoriasis reported that long-term FAE therapy seemed to be effective and safe in daily practice.[30] In this particular study, PASI was available in 59 patients at baseline and improved from 17.3 (mean) at baseline to 9.0 (n = 54) at 3 months and further improved to 4.8 (n = 22) at 36 months. At least one FAE-related AE was reported in 28.4% of patients (n = 36), mostly gastrointestinal complaints and flushing. SAEs did not occur.[30]

Gradually, more evidence on the efficacy and safety of FAE in pediatric psoriasis becomes available. Currently, a prospective, placebo-controlled study on the efficacy and safety of FAE in children (aged 10 to 17 years) is ongoing in Germany.[30,31] Apart from the reassuring data that have become available in the recent literature, there is an increased concern about the possibility of FAE-induced lymphocytopenia and the described manifestation of progressive multifocal leukoencephalopathy (PML) in adults.[32-41] Therefore, it is extremely important to obtain prospective, long-term safety data in this vulnerable age group, and to abide by the recommendations from the updated European S3-guideline on FAE-induced leukocytopenia and/or lymphocytopenia.[42]

Apart from the evidence we have added to the literature in the past few years, other publications on conventional systemic and biologic treatments in pediatric psoriasis have appeared, of which most important evidence will be discussed below. The evidence on cyclosporine has augmented since publication of our systematic review (**Chapter 2.2)**. The majority of new evidence comes from three recently published retrospective studies with a total of 85 children.[43-45] In these studies, treatment duration varied between 1-24 months and cyclosporine seemed to show acceptable efficacy and safety data.[43-45] Only one study used PASI as a severity measure and reported achievement of PASI 75 in 39.5% of patients at week 16, whereas another 39.5% were non-responders.[43] Long-term safety data were not available.

In addition to the conventional systemic treatments, the evidence on biologicals in pediatric psoriasis has also largely increased. To date, etanercept, adalimumab and ustekinumab are licensed for use in pediatric psoriasis[43], while at the start of this thesis, etanercept was the only approved biological. Etanercept is licensed to treat chronic severe plaque-type psoriasis in children and adolescents aged six years and older in case of an inadequate response to, or intolerance to, other systemic therapies or phototherapy.[43,46,47] Its evidence was primarily based on a double-blind, multicenter, phase III RCT in 211 children and adolescents (aged 4-17 years) with plaque-type psoriasis.[48] One hundred and six children were treated with once-weekly subcutaneous injections of etanercept 0.8 mg/kg (maximum 50 mg).[48] At week 12, PASI 75 was achieved in 57% of patients. During the open-label part of the study, four SAEs (of which three infections) occurred in three patients which all resolved without sequelae.[48] Long-term safety and efficacy data with a follow-up period of 264 weeks have been described in the literature just now.[49] The number of patients remaining on the study at week 264, however, was small.[49] Through week 264, AEs occurred in 89.0% of patients, mostly infections, whereas malignancies or opportunistic infections did not occur. Efficacy at week 264 was maintained.[49] At the moment, a post-authorization safety study on the long-term safety and efficacy of etanercept in pediatric psoriasis patients (PURPOSE) in several centers in Europe is still ongoing.[47,50]

In 2015, adalimumab and ustekinumab, have been approved in Europe for use in the pediatric psoriasis population. Adalimumab has been registered by the European Medicines Agency (EMA) for the treatment of severe chronic plaque-type pediatric psoriasis patients (age ≥4 years) who have had an inadequate response to, or are inappropriate candidates for topical therapy and phototherapy.[43,51] A recent multicenter, randomized, double-blind study evaluated two doses of adalimumab (0.8 mg/kg up to 40 mg and 0.4 mg/kg up to 20 mg, at week 0 and then every other week from week 1) versus MTX in 114 pediatric patients with severe chronic plaque-psoriasis.[27-29,52] In the 38 patients treated with adalimumab 0.8 mg/kg, PASI 75 at week 16 was achieved in 57.9% of patients. AEs occurred in 68.4% of the patients through 16 weeks, mostly infections (47.4%). There

were no deaths, malignancies or SAEs.[28] However, long-term safety data in pediatric psoriasis patients are lacking.

Ustekinumab is the other biological which has been approved since June 2015 for the treatment of moderate-to-severe plaque-type psoriasis in adolescents aged 12 years and older who are inadequately controlled by, or are intolerant to phototherapy or other systemic therapies.[43,53] In a recent phase III, multicenter, double-blind RCT on 110 patients (aged 12-17 years), 36 patients were treated with standard dosage ustekinumab (0.75 mg/kg [≤60 kg], 45 mg [>60-≤100 kg], and 90 mg [>100 kg]) at weeks 0 and 4 and every 12 weeks through week 40. At week 12, PASI 75 was achieved in 80.6% of patients, whereas AEs were reported in 44.4% of patients, mostly infections.[54]

To date, the literature about these three biologicals accounts for the largest body of evidence on systemic treatments in pediatric psoriasis.[26,28,48,49,52,54-58] Although these biologicals in general showed large efficacy and a reasonably safety profile, caution should be taken to the relative lack of long-term safety data in children and adolescents with psoriasis. In patients with juvenile idiopathic arthritis (JIA), however, biological treatment has been used for about 15 years[25] and long-term safety data on etanercept up to 14 years are available.[25,59,60] Major areas of concern with respect to treatment with biologics include the risk on infusion and injection reactions, development and aggravation of infections and limited antibody production in case of vaccinations, occurrence of a second autoimmune disease, cytopenias and the development of malignancies, particularly lymphoma.[25] Although some cases of lymphomas and other malignancies have been described in pediatric patients with arthritis, inflammatory bowel diseases or sarcoidosis treated with tumour necrosis factor-α (TNF-α) blockers,[25,47,61,62] to date the assessment of causality is not clear. Confounding factors include the unknown potential risk on malignancy of the underlying diseases and the use of other immunosuppressive medication.[47,61-63] The association between the use of TNF-α blockers and the risk on lymphoma and other malignancies or the development of a second autoimmune disease in pediatric psoriasis patients is still unknown. Therefore, more long-term safety data are indispensable and the benefits and risks of a biologic treatment in pediatric psoriasis should be weighted carefully, and discussed with the children and their caregivers.[64]

In conclusion, given the newly retrieved evidence on both conventional systemic treatments and biologicals, the proposed treatment algorithm stated in **Chapter 2.2** needs more consideration. In this respect, long-term safety data are pivotal. Given the fact that long-term safety data in this vulnerable group are very important and in JIA a track record of long-term use on MTX is available[60,65-72], we consider MTX as the preferential conventional systemic treatment in pediatric psoriasis. Although gradually more evidence has appeared on FAE in pediatric psoriasis, suggesting it to be an effective treatment option, there is increased concern about the potential of FAE-induced lymphocytopenia

and its possible manifestation of PML in adults. Furthermore, evidence on its long-term safety and efficacy in children and adolescents is still limited. Therefore, the position of FAE in the systemic treatment of pediatric psoriasis should still be after treatment with MTX. In pustular or erytrodermic psoriasis, retinoids could be considered. The available evidence on cyclosporine is still limited and only retrospectively collected. Therefore, and because of the nephrotoxic potential of cyclosporine[73] and the relative lack on long-term safety data, prospective studies are warranted in order to define more clearly the position of cyclosporine in the treatment of pediatric psoriasis. Biologicals are effective in pediatric plaque-type psoriasis[28,48,54], but long-term safety data are limited, although the safety data of five-year etanercept in pediatric psoriasis and 14-year etanercept in JIA are reassuring. Caution should be taken to the unclear association between TNF-α blockers and the development of malignancies (particularly lymphoma) and other autoimmune diseases. Therefore (and also because of the high costs), we suggest biologicals to be a third-line drug and recommend a balanced discussion of risks and benefits in patients and parents.

Aim 5: To explore the efficacy of an outpatient multidisciplinary training programme for children and adolescents with psoriasis and their parents.

In **Chapter 2.5** we described a pilot study on the effects of an outpatient multidisciplinary training programme for children and adolescents with psoriasis and their parents. Satisfaction with the programme was found to be high and was observed to be higher in younger children and their parents compared to adolescents and their parents. In both participants and age- and sex-matched controls, the outcomes on the self-reported questionnaires (CDLQI[74], ISDL[75], SIFS[76] and DFI[77]) showed positive changes after training and at three-month follow-up, whereas psoriasis severity (PASI) hardly changed.

Although the training programme generally was well-accepted and positively evaluated by patients and parents, results on the self-reported questionnaires seemed to be somewhat disappointing. An explanation could be the selection of patients. Patients who are at risk for psychological adjustment problems might obtain more benefit from psychological support. Second, apart from the CDLQI, the self-reported questionnaires used in this pilot study were not validated for use in children with psoriasis. Possibly, these questionnaires were not sensitive enough to detect changes in children.

QoL in children and adolescents with psoriasis can be detrimental affected,[78-83] and early-onset psoriasis is reported to be associated with depression[84,85] and anxiety.[85] In addition, also in the caregivers of children with psoriasis anxiety and depression are frequently observed.[86] Therefore, psychosocial support for patients and parents is essential. To our knowledge, one study described the efficacy of an educational programme in 34 pediatric psoriasis patients, which was performed in an inpatient setting.[87] Direct comparison with our study is, however, not possible due to differences in programme design and assessment measures.

In particular the contact with peers in group format was assessed as being very useful by both the patients and their parents in our study. This suggests the preference for psychological support in a group format. However, the question arises whether other forms of psychological support might be more optimal in children and adolescents with psoriasis and their parents. Satisfaction with our programme was lower in adolescents. In addition, adolescents were less willing to participate in the programme. Especially in adolescents, telepsoriasis services e.g. internet-based interventions[88,89] including online support communities[90], might be valuable. Internet-based interventions might be more convenient and flexible due to its potential of reducing waiting lists and traveling time. In addition, it could be an option for patients who did not want to participate in face-to-face groups because of feelings of shame or stigmatization of needing psychological support. Consequently, a larger number of patients could be reached.[88,89] Furthermore, mobile-phone-based interventions could be useful to improve adherence.[5,91] Apart from face-to-face training groups delivered by trained dermatologists and/or psychologists, other potential forms of psychological support might include interventions by specialized dermatology nurses[92-94] (eventually in day-care setting), or camps.[95]

Assessment measures on disease severity and psychosocial impact

For optimal therapeutic decision-making clinicians should take both the assessment of disease severity as well as the impact of psoriasis on the patients' lives into account. To quantify psoriasis severity and the impact on physical, psychological and social functioning of those affected as precisely as possible, reliable and valid assessment measures are needed. Nowadays, the PASI[96] is the most commonly used psoriasis severity measure[73,97-99], whereas the CDLQI[74] and the Dermatology Life Quality Index (DLQI)[100] are widely used *dermatology-specific* questionnaires to assess the impact of skin diseases on QoL in children (4-16 years) and adults (≥ 16 years) respectively.

In scientific literature, there is some debate on the correct use of the term 'outcome measures', which intrinsically should be able to detect changes as a result of treatment (e.g. PASI 75), whereas 'severity measures' focus on the assessment of disease severity (e.g. PASI).[98,101] In this respect, it might be more appropriate to use the term 'assessment measures' or 'assessment tools' instead of 'outcome measures'.[101] Consequently, this might also apply for the term 'patient-reported assessment measures' or 'patient-reported assessments' instead of the commonly used term 'patient-reported outcome (PRO) measures´. A PRO is defined by the Food and Drug administration (FDA) as 'any report of the status of a patient's health condition that comes directly from the patient, without interpretation of the patient's response by a clinician or anyone else'.[101,102] In addition, there are also questionnaires available which assess the impact on the lives of partners, parents or other family members and are therefore not strictly 'patient-reported'[103], like

the SIFS[76] or DFI[77] which both are used in **Chapter 2.5** of this thesis to assess the impact on family life.

Nevertheless, in scientific literature the term 'outcome measures' is often used interchangeably for both the detection of changes as a result of treatment and for the assessment of the severity itself.[101] For the assessment of severity itself however, 'assessment measure' would be more appropriate.[101] In the introduction and discussion of this thesis, the term 'assessment measures' will be used to describe assessment of disease severity and/or psychosocial impact. It has to be noted that in some articles included in this thesis, the term 'outcome measures' has been used, although the term 'assessment measures' would probably be more appropriate.

Aim 6: To develop a refined PASI score for patients with small affected areas (Low PASI).

As a response on the frequently described criticism that PASI is not able to assess small involved areas,[98,104-107] we developed a refined PASI score for psoriasis patients with small affected areas in a body region (<10% of a body region), called the Low PASI score. In **Chapter 3.1** the Low PASI score is presented and the scores obtained with the Low PASI (measured by two independent investigators) are compared to the classic PASI scores. In both investigators, the Low PASI was significantly lower (1.71 and 1.76) than the classic PASI (4.14 and 4.33 respectively). Furthermore, in both scores the interobserver agreement was excellent for both investigators (ICC classic PASI = 0.95 and Low PASI = 0.87).

PASI however, has been most extensively studied and is most widely used in a research setting as was concluded in two systematic reviews from 2010.[97,98] In addition, it is often used as a standard reference to validate new severity measures.[97-99] It has to be noted that in the Low PASI score, all principles of the classic PASI are preserved except for the area score <10% which is dived into four fractional components. Therefore, the Low PASI aimed to refine the classic PASI score in small involved areas by allowing more possible scores at lower levels of psoriasis extent, and it does not pretend to replace the classic PASI. Furthermore, from our experience, Low PASI is a quick tool which will be easy to learn for experienced PASI-assessors.

Based on this pilot study, we feel that the Low PASI could be a valuable instrument in the assessment of psoriasis severity in small involved areas. As nowadays the therapeutic arsenal has expended and highly effective psoriasis treatments have become available, there is an increasing need for measures to assess severity of psoriasis as precisely as possible when only a small body area of the patient is affected. However, as this was only a pilot study with a sample size of 10 participants with psoriasis, further research in much larger psoriasis populations is needed before implementation can take place.

Aim 7: To compare DLQI and CDLQI scores in psoriasis patients aged 16-17 years.

In **Chapter 3.2** DLQI and CDLQI scores in 56 patients with psoriasis aged 16-17 years were compared. Although DLQI and CDLQI scores closely correlated ($r = 0.90$, $p < 0.001$), the mean DLQI score (5.41 ± 5.20) was lower than the mean CDLQI score (6.61 ± 5.74) ($p < 0.001$). This difference was mainly caused by the low score related to sexual difficulties in the DLQI (0.11 ± 0.49) and the high score regarding sleep in the CDLQI (0.71 ± 0.93). Furthermore, the questions in the DLQI regarding sports and work/study scored lower than the questions on sports and school/holiday in the CDLQI respectively.

The DLQI[100] and the CDLQI[74] are widely used *dermatology-specific* questionnaires to assess QoL and are validated in adults (patients aged ≥ 16 years) and children (4-16 years) with a variety of skin diseases respectively. As adolescents are a unique group who have to deal with specific QoL concerns, the nature and extent of the impact of skin diseases on their QoL may be different compared to children or adults.[108] From our study, in which only patients aged 16-17 years with psoriasis were included, both the DLQI and CDLQI probably did not to capture all QoL issues which might be important in this specific age range. For example, both sexuality[108,109] (low score in the DLQI) and sleep[108] (high score in the CDLQI) may be important QoL issues for adolescents, although the importance of sexual difficulties could not be confirmed in our study.

Psoriasis-specific QoL measures specifically designed for use in adolescents in this age range are not available, and the only validated *psoriasis-specific* QoL measure for children is the Scalpdex, which has been validated in Dutch pediatric patients (aged 6-18 years) with scalp psoriasis.[110] In adolescents however, there are some *dermatology-specific* instruments to assess the QoL impact of skin diseases, like the Skindex-Teen[111] and Teenagers' Quality of Life (T-QoL©) Index.[112] As both the Skindex-Teen[111] and the T-QoL[112] have been designed and validated specifically for adolescents and include more items on psychosocial functioning[111] and self-image and psychological impact[112] respectively, these instruments might be more sensitive for patients aged 16-17 years than either the DLQI or CDLQI. Theoretically, when assessing QoL, it would be most appropriate to use validated QoL measures specified to several age ranges. It is however, questionable whether such approach would be realistic and applicable in a daily clinical practice setting. An advantage of the DLQI and CDLQI is that both are easy to use with an average completion time of two minutes.[113,114] From a practical point of view therefore, the use of these relatively quick and well-known *dermatology-specific* questionnaires is more feasible, taking into account its limitations when given to adolescents. The DLQI and CDLQI could be used as a first screening instrument to point out the presence of QoL issues. Additionally, for adolescents whose QoL seemed to be impaired, further in-depth investigation could take place with specific age suitable measures.

Aim 8: To investigate the criterion validity, construct validity, and response distribution of the severity (SPI-s) and psychosocial impact (SPI-p) domains of the professional (proSPI) and self-assessment (saSPI) versions of SPI in children and adolescents with psoriasis.

This aim has been described in **Chapter 3.3** in 113 children and adolescents with psoriasis with a median age of 12.0 years (range 4-17 years). ProSPI-s was closely correlated with PASI (r = 0.87), whereas the correlation between saSPI-s and PASI was lower (r = 0.69). The correlation between the two psychosocial impact measures (SPI-p and CDLQI) was 0.78. Furthermore, the correlation between these two psychosocial impact measures (SPI-p and CDLQI) and saSPI-s was higher than the correlations of these two impact measures with either PASI or proSPI-s. In both proSPI-s and SPI-p the full range of scores was obtained, whereas the highest saSPI-s score was 30 (maximum 50).

At the moment, it is too early to recommend whether PASI, CDLQI and/or SPI should be the assessment measures of preference in clinical trials and/or routine clinical practice in pediatric psoriasis. It has to be noted that the SPI-p encompasses only a visual analogue scale line giving the professional an overall assessment of psychosocial impairment. This is in contrast to the CDLQI[74], which gives additional information on which aspects of QoL are impaired. Consequently, we feel that SPI-p cannot replace the CDLQI. In routine clinical practice, however, SPI-p can be readily introduced as a very quick instrument to assess the psychosocial impact of psoriasis in children and adolescents. Furthermore, in clinical studies, the saSPI proforma could give the health professional valuable additional information on patients' and/or parents' perception of their disease.

Main conclusions

Treatments (Chapter 2)

- Treatment of mild-to-moderate pediatric psoriasis with calcipotriol/betamethasone dipropionate ointment in daily clinical practice yielded a mild improvement in psoriasis severity. Its effect maintained during 24 weeks of follow-up. *(Chapter 2.1)*
- Evidence on the efficacy and safety of systemic treatments in pediatric psoriasis was limited and mostly of low level. Of the conventional systemic treatments, most data were available on methotrexate, while etanercept had the largest body of evidence on biologic treatment in pediatric psoriasis. Apart from 96-weeks safety and efficacy data on etanercept, long-term safety data were not available. *(Chapter 2.2)*
- Treatment with methotrexate in 25 children and adolescents with plaque-type psoriasis demonstrated a positive effect on psoriasis severity, improved quality of life and showed a reasonable safety profile in daily clinical practice. *(Chapter 2.3)*
- Treatment of 14 pediatric psoriasis patients with fumaric acid esters in daily clinical practice resulted in an improvement of disease severity and quality of life in the majority of patients. Side effects occurred frequently, but were usually mild and transient. *(Chapter 2.4)*
- An outpatient multidisciplinary training programme for children and adolescents with psoriasis and their parents was well-accepted and positively evaluated. *(Chapter 2.5)*

Assessment measures (Chapter 3)

- A refined PASI score for small involved areas (Low PASI) was developed. It allowed more possible scores at lower levels of psoriasis extent compared to the classic PASI. *(Chapter 3.1)*
- In psoriasis patients aged 16-17 years, DLQI and CDLQI scores closely correlated. The mean DLQI score was lower than the mean CDLQI score. *(Chapter 3.2)*
- In pediatric psoriasis, the modified children's proSPI and saSPI were shown to be valid and usable. *(Chapter 3.3)*

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Chapter 5

Nederlandse samenvatting

Dit proefschrift over kinderen en adolescenten met psoriasis bestaat uit twee delen: behandelingen bij kinderen en adolescenten met psoriasis en uitkomstmaten. Het overkoepelende doel van het eerste deel was het verwerven van meer inzicht in de veiligheid en effectiviteit van een aantal behandelingen bij kinderen en adolescenten met psoriasis, te weten calcipotriol/ betamethasondipropionaat zalf, methotrexaat, fumaraten en een multidisciplinair trainingsprogramma. In het tweede deel van dit proefschrift staan uitkomstmaten ter beoordeling van de ernst van psoriasis en/of psychosociale impact centraal. Uiteindelijk heeft dit geleid tot acht publicaties die hieronder kort worden samengevat en waarvan de belangrijkste conclusies worden besproken.

De meeste data die gebruikt zijn in dit proefschrift zijn afkomstig van de gegevens die verzameld zijn in de Child-CAPTURE. In deze prospectieve database worden sinds 2008 gegevens verzameld uit de dagelijkse praktijk over de effectiviteit, veiligheid en invloed op kwaliteit van leven (KvL) van alle kinderen en adolescenten met psoriasis die op onze polikliniek worden gezien op twee kinderpsoriasis spreekuren. Op dit moment zijn 340 kinderen geïncludeerd en de inclusie van patiënten duurt nog steeds voort.

Het eerste deel van dit proefschrift **(hoofdstuk 2)** bestaat uit vijf studies over therapeutische interventies bij kinderen en adolescenten met psoriasis. In **hoofdstuk 2.1** onderzochten wij prospectief de effectiviteit, veiligheid en invloed op KvL van calcipotriol/ betamethasondipropionaat zalf in 73 kinderen en adolescenten met psoriasis in de dagelijkse praktijk. De mediane behandelingsduur was 35 weken (variërend van 1-176 weken). Op week 12 was de gemiddelde Psoriasis Area and Severity Index (PASI) verbeterd van 5.2 naar 4.4 (15.4%). Dit effect bleef behouden na 24 weken behandeling (PASI 4.3, 17.3% verbetering). De mediane Children's Dermatology Life Quality Index (CDLQI) verbeterde significant van 5.5 naar 4.0 na 12 weken behandeling en de visual analogue scale (VAS) scores voor pijn en jeuk waren gedaald. Er werden bij vijf patiënten (7%) bijwerkingen beschreven, die mogelijk aan de behandeling gerelateerd waren. Vier van deze vijf patiënten hadden striae. Er werden geen ernstige bijwerkingen gevonden.

In **hoofdstuk 2.2** wordt een systematisch *review* over de effectiviteit en veiligheid van systemische behandelingen bij kinderen met psoriasis gepresenteerd. In dit *review* werd gekeken naar de beschikbare *evidence* in de literatuur tot maart 2014. Van de conventionele systemische behandelingen waren de meeste gegevens beschikbaar over methotrexaat. Deze studies waren echter retrospectief en hadden een lage bewijskracht. Er werden vooral enkele nieuwe publicaties over fumaraten gevonden. Maar ook deze studies waren retrospectief en beschreven een klein aantal patiënten. Van alle systemische behandelingen had etanercept de meeste *evidence*. Op basis van dit *review* concludeerden wij dat de beschikbare *evidence* over de effectiviteit en veiligheid van systemische behandelingen bij kinderen met psoriasis beperkt was. Er waren nauwelijks prospectieve studies en de meeste publicaties hadden een lage bewijskracht. Bovendien waren er

geen gegevens beschikbaar over de lange termijn veiligheid, met uitzondering van een publicatie over de veiligheid en effectiviteit van etanercept na 96 weken behandeling.[1]

Aangezien de beschikbare *evidence* over de conventionele systemische behandelingen beperkt was en retrospectief verzameld, besloten wij het gebruik van methotrexaat (**hoofdstuk 2.3**) en fumaraten (**hoofdstuk 2.4**) bij kinderen en adolescenten met psoriasis te analyseren door gebruik te maken van onze prospectieve database. In **hoofdstuk 2.3** onderzochten wij de effectiviteit, veiligheid en de invloed op KvL van methotrexaat bij 25 kinderen met psoriasis in de dagelijkse praktijk. De behandelingsduur varieerde van 12.6 tot 163.4 weken (mediaan 60.4 weken). Een verbetering in PASI van 75% of meer (PASI 75) werd bereikt in 4.3%, 33.3%, 40% en 28.6% van de patiënten op week 12, 24, 36 en 48, respectievelijk. De mediane PASI verbeterde van 10.0 (range 3.8-42.4) bij start naar 4.3 (range 0-19.8) op week 24, terwijl de mediane CDLQI score daalde van 9 (range 2-20) naar 3.8 (range 0-21). MTX leek een redelijk veiligheidsprofiel te hebben. De meest frequent gerapporteerde bijwerkingen waren ernstige misselijkheid (n = 5), infecties met noodzaak voor antibiotica of antivirale medicatie (n = 5) en ernstige vermoeidheid (n = 4). De enige ernstige bijwerking was een longontsteking waarvoor ziekenhuisopname. Deze verbeterde zonder consequenties.

In **hoofdstuk 2.4** wordt een prospectieve studie beschreven waarin 14 kinderen en adolescenten met recalcitrante plaque psoriasis werden behandeld met fumaraten in de dagelijkse praktijk. De behandelingsduur varieerde van 12 tot 124 weken, met een mediaan van 48.6 weken. Behandeling met fumaraten resulteerde in een verbetering in de ernst van de psoriasis en KvL in de meerderheid van de patiënten. De gemiddelde PASI (±SEM) verbeterde van 10.5 (1.0) bij start naar 8.6 (1.1), 6.2 (1.6) en 4.9 (1.5) op week 12, 24 en 36, terwijl de gemiddelde CDLQI (±SEM) verbeterde van 8.9 (1.4) bij start naar 6.8 (1.2), 3.7 (1.4) en 3.1 (2.0), respectievelijk. Hoewel bijwerkingen frequent voorkwamen, waren zij meestal mild en tijdelijk van aard. De meest frequent gerapporteerde bijwerkingen waren maag-darmklachten (n = 13, 92.9%) en opvliegers (n = 10, 71.4%), terwijl lymfocytopenie (n = 5, 45.5%) en eosinofilie (n = 4, 36.4%) de meest voorkomende lab afwijkingen waren. Er werd één ernstige bijwerking gerapporteerd; deze was niet gerelateerd aan de behandeling met fumaraten.

Voor de discussie van dit proefschrift werd de literatuur over systemische behandelingen bij kinderen met psoriasis bestudeerd die tussen maart 2014 en januari 2016 was verschenen, zodat het bestaande *review geüpdate* werd. Aan de hand van het systematische *review* beschreven in **hoofdstuk 2.2** en de nieuw gevonden literatuur werd het volgende behandelingsalgoritme voorgesteld. De lange termijn veiligheid was bij het bepalen van het algoritme zeer belangrijk. Van de conventionele systemische middelen zijn de meeste prospectieve gegevens beschikbaar over methotrexaat.[2,3] Bovendien wordt methotrexaat bij kinderen met juveniele idiopathische artritis (JIA) al sinds decennia gebruikt, met een acceptabel veiligheidprofiel.[4-10] Derhalve beschouwen wij methotrexaat als de eerste keus conventionele systemische behandeling bij kinderen met psoriasis. Geleidelijk is er

meer *evidence* beschikbaar gekomen over fumaraten als effectieve behandeloptie voor kinderen met psoriasis.[11-13] Er bestaat echter toegenomen bezorgdheid over de mogelijkheid van een door fumaraten geïnduceerde lymfocytopenia en een mogelijke manifestatie van progressieve multifocale leukoencephalopathie (PML) bij volwassenen.[14-23] Bovendien zijn er slechts beperkte gegevens beschikbaar over de lange termijn veiligheid en effectiviteit van fumaraten bij kinderen en adolescenten. Derhalve achten wij de positie van fumaraten in het behandelalgoritme van systemische behandelingen bij kinderen met psoriasis na die van methotrexaat. Bij pustuleuze of erytrodermatische psoriasis kan behandeling met retinoiden worden overwogen. De meeste *evidence* over ciclosporine als behandeloptie bij kinderen met psoriasis bestaat uit een beperkt aantal recent gepubliceerde retrospectieve studies.[24-26] Bovendien kan ciclosporine een nefrotoxisch effect hebben[27] en zijn gegevens over de lange termijn veiligheid beperkt. Derhalve zijn prospectieve studies noodzakelijk om meer inzicht te krijgen in de positie van ciclosporine in de systemische behandeling van kinderen met psoriasis. Biologicals zijn effectief bij kinderen met plaque psoriasis.[2,28,29] Gegevens over de lange termijn veiligheid zijn echter beperkt; hoewel de data van vijf-jaar behandeling met etanercept bij kinderen met psoriasis[30] en 14-jaar behandeling met etanercept bij kinderen met JIA[31-33] een geruststellend veiligheidsprofiel laten zien. Voorzichtigheid is geboden gezien de onduidelijke associatie tussen TNF-α blockers en de ontwikkeling van maligniteiten (in het bijzonder lymfoom), die beschreven worden bij kinderen met artritis, inflammatoire darmziekten of sarcoidosis, en de ontwikkeling van andere auto-immuunziekten.[31,34-37] Derhalve (en ook vanwege de hoge kosten) beschouwen wij biologicals als een derdelijns behandeling en adviseren wij een gebalanceerde afweging van de voor- en nadelen in overleg met kinderen en adolescenten en ouders.[38]

Naast medicamenteuze behandeling zijn educatie en psychosociale steun een belangrijke additionele behandelingsinterventie.[39-41] In **hoofdstuk 2.5** exploreerden wij in een *pilotstudy* de effecten van een poliklinisch multidisciplinair trainingsprogramma voor kinderen en adolescenten met psoriasis en hun ouders op de tevredenheid van patiënten en ouders, KvL, jeuk en krabben, ziektecognities en invloed op het gezin. De tevredenheid met het programma was hoog bij zowel patiënten als ouders. Jongere kinderen en hun ouders waren meer tevreden dan adolescenten en hun ouders. De uitkomsten van de zelfgerapporteerde vragenlijsten [CDLQI[42], Impact of Chronic Skin Disease on Daily Life (ISDL)[43], Stein Impact on Family Scale (SIFS)[44] en Dermatitis Family Impact Questionnaire (DFI)[45]] vertoonden positieve veranderingen na de training en bij drie-maanden follow-up bij zowel de deelnemers als bij op leeftijd- en geslacht gematchde controles. De ernst van de psoriasis (PASI) veranderde nauwelijks.

Het tweede deel van dit proefschrift **(hoofdstuk 3)** bestaat uit drie studies over uitkomstmaten ter beoordeling van de ernst van de psoriasis en/of psychosociale impact. Wij ontwikkelden een verfijnde PASI score voor patiënten met psoriasis bij wie een klein

deel van het lichaamsoppervlak (<10% van een lichaamsregio) is aangedaan, de Low PASI. In **hoofdstuk 3.1** presenteerden wij de Low PASI score en vergeleken wij de scores verkregen met de Low PASI (gemeten door twee onafhankelijke onderzoekers) met de scores van de klassieke PASI. In beide onderzoekers was de Low PASI significant lager (1.71 en 1.76) dan de klassieke PASI (4.14 en 4.33, respectievelijk). Bovendien was de *interobserver agreement* in beide scores uitstekend voor beide onderzoekers (ICC klassieke PASI = 0.95 en Low PASI = 0.87).

In **hoofdstuk 3.2** vergeleken wij twee dermatologiespecifieke vragenlijsten om de KvL te meten in 56 patiënten met psoriasis in de leeftijd van 16-17 jaar: de Dermatology Life Quality Index (DLQI)[46] en de CDLQI.[42] De CDLQI is gevalideerd voor kinderen met huidaandoeningen in de leeftijd van 4-16 jaar[42], terwijl de DLQI is gevalideerd voor patiënten van 16 jaar en ouder.[46] Hoewel de DLQI en CDLQI scores nauw correleerden ($r = 0.90$, $P < 0.001$), was de gemiddelde DLQI score (5.41 ± 5.20) lager dan de gemiddelde CDLQI score (6.61 ± 5.74) ($P < 0.001$). Dit verschil werd voornamelijk veroorzaakt door de lage score op de vraag naar seksuele problemen in the DLQI (0.11 ± 0.49) en de hoge score op de vraag naar slaap in de CDLQI (0.71 ± 0.93). Tevens scoorden de vragen in de DLQI over sport en respectievelijk werk/studie lager dan de vragen over sport en school/vakantie in de CDLQI.

De Simplified Psoriasis Index (SPI) is een nieuwe uitkomstmaat die zowel de ernst van de psoriasis als de psychosociale impact beoordeeld.[47] De SPI kan worden ingevuld door de zorgprofessional (proSPI) of door de patiënt zelf (saSPI). De SPI is gevalideerd bij volwassenen met psoriasis.[47] **Hoofdstuk 3.3** beschrijft de validatie van de ziekte-ernst (SPI-s) en psychosociale impact (SPI-p) domeinen van de proSPI en de saSPI in 113 kinderen en adolescenten met psoriasis. De proSPI-s correleerde nauw met de PASI ($r = 0.87$), terwijl de correlatie tussen de saSPI-s en de PASI lager was ($r = 0.69$). De correlatie tussen de twee psychosociale impact maten (SPI-p en CDLQI) was 0.78. In zowel de proSPI-s als SPI-p kwam het volledige bereik van de scores voor, terwijl de hoogste saSPI-s score 30 was (maximum 50). Een voordeel van de SPI boven andere uitkomstmaten is het feit dat hierin een ernstmaat en een psychosociale maat worden gecombineerd, terwijl de uitkomsten wel apart te interpreteren zijn.[47]

Belangrijkste conclusies

Behandelingen (hoofdstuk 2)

- Behandeling van mild tot matig ernstige psoriasis bij kinderen en adolescenten met calcipotriol/ betamethasondipropionaat zalf in de dagelijkse praktijk resulteerde in een milde verbetering in de ernst van psoriasis. Dit effect bleef gehandhaafd na 24 weken. *(Hoofdstuk 2.1)*
- De *evidence* over de effectiviteit en veiligheid van systemische behandelingen bij kinderen met psoriasis was beperkt en meestal van lage bewijskracht. Van de conventionele systemische behandelingen waren de meeste gegevens beschikbaar over methotrexaat, terwijl van de biologicals de meeste *evidence* beschikbaar was over etanercept. Met uitzondering van een publicatie naar de veiligheid en effectiviteit van etanercept gedurende 96 weken behandeling, waren er geen gegevens beschikbaar over de lange termijn veiligheid. *(Hoofdstuk 2.2)*
- Behandeling met methotrexaat in 25 kinderen en adolescenten met plaque psoriasis in de dagelijkse praktijk had een positief effect op de ernst van de psoriasis, verbeterde de kwaliteit van leven en vertoonde een redelijk veiligheidsprofiel. *(Hoofdstuk 2.3)*
- Behandeling van 14 kinderen en adolescenten met psoriasis met fumaraten in de dagelijkse praktijk resulteerde in een verbetering van ziekte ernst en kwaliteit van leven in de meerderheid van de patiënten. Bijwerkingen kwamen frequent voor, maar waren meestal mild en tijdelijk van aard. *(Hoofdstuk 2.4)*
- Een poliklinisch multidisciplinair trainingsprogramma voor kinderen en adolescenten met psoriasis en hun ouders werd goed geaccepteerd en positief beoordeeld. *(Hoofdstuk 2.5)*

Uitkomstmaten (hoofdstuk 3)

- Een verfijnde PASI score voor patiënten met psoriasis bij wie een klein deel van het lichaamsoppervlak is aangedaan (Low PASI) werd ontwikkeld. De Low PASI beschikt over meer potentiële scores dan de klassieke PASI indien een klein deel van het lichaamsoppervlak is aangedaan. *(Hoofdstuk 3.1)*
- In patiënten met psoriasis in de leeftijd van 16-17 jaar correleerden de DLQI en CDLQI scores nauw. De gemiddelde DLQI score was lager dan de gemiddelde CDLQI score. *(Hoofdstuk 3.2)*
- Bij kinderen en adolescenten met psoriasis waren de voor kinderen gemodificeerde proSPI en saSPI valide en bruikbaar. *(Hoofdstuk 3.3)*

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Chapter 6

6.1 List of publications

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6.2 Curriculum Vitae

Maartje Johanna van Geel werd op 3 juli 1987 geboren te Boxtel. Nadat zij in 2005 het gymnasiumdiploma cum laude behaalde aan het Jacob-Roelandslyceum te Boxtel, startte zij met de studie Geneeskunde aan de Radboud Universiteit Nijmegen. In januari 2012 behaalde zij het artsexamen cum laude. In 2012 was zij gedurende een half jaar werkzaam als arts-assistent op de afdeling Reumatologie van ziekenhuis Rijnstate te Arnhem en Velp. In november van datzelfde jaar startte zij als arts- onderzoeker op de afdeling Dermatologie van het Radboud universitair medisch centrum te Nijmegen onder supervisie van dr. E.M.G.J. de Jong. In april 2013 begon zij op dezelfde afdeling met haar promotieonderzoek naar psoriasis bij kinderen en adolescenten onder begeleiding van copromotor dr. M.M.B. Seyger en promotoren prof. dr. dr. P.C.M. van de Kerkhof en prof. dr. E.M.G.J. de Jong.

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